PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

FDA White Oak Campus
10903 New Hampshire Ave.
Bldg. 31, Conference Center
Silver Spring, MD

March 21, 2013

PROBUPHINE
(buprenorphine hydrochloride subdermal implant) for maintenance treatment of opioid dependence

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FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Psychopharmacologic Drugs Advisory Committee

PROBUPHINE (buprenorphine hydrochloride subdermal implant) for maintenance treatment of opioid dependence

March 21, 2013

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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products

MEMORANDUM

DATE: February 1, 2013

FROM: Bob A. Rappaport, Division Director
Division of Anesthesia, Analgesia, and Addiction Products

TO: Chair, Members, and Invited Guests, Psychopharmacologic Drugs Advisory Committee (PDAC)

RE: Overview of the March 21, 2013 PDAC Meeting to discuss NDA 204442 for Probuphine (buprenorphine subdermal implant) for treatment of opioid dependence

At this meeting of the Psychopharmacologic Drugs Advisory Committee, we will be discussing a new drug application (NDA) 204442, for Probuphine (buprenorphine subdermal implant) submitted by Titan Pharmaceuticals, Inc., for the treatment of opioid dependence.

During this meeting, representatives from the Agency and the Applicant will present:

- Data from the clinical trials performed to assess the efficacy and safety of Probuphine in the treatment of opioid-dependent patients:
    - While the study design (randomized, placebo-controlled, parallel group study of 6-months duration) is not novel, some of the analytic approaches and concepts are.
    - Because the systemic safety of buprenorphine has been characterized, the safety presentation will emphasize information about adverse events associated with the surgical implantation and removal procedures.
- Information about the safety experience with other implantable products:
    - Probuphine requires surgical implantation and removal, similar to the implantable contraceptive product, Norplant. Because the safety experience with Probuphine itself is very limited, we will draw upon

information about the experience with Norplant to help understand the risks.

- The Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS)

Following these presentations, you will be asked to assess these findings and to discuss the adequacy of the data from four key areas intended to support approval of this application:

1. We will ask the committee to address whether the efficacy data provide evidence of a clinically significant effect on patients' drug use behavior, and whether adequate dose exploration has been conducted to identify an effective dose.

2. We will ask the committee to discuss whether the Applicant has adequately characterized the safety profile of the Probuphine implant in this patient population, commenting both on the safety of the product in general, as well as on the specific safety aspects related to the placement and removal of the implants.

3. We will ask the committee to discuss whether the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for providers who will implant the product, is adequate to address the risks of potential implantation procedure complications. We will ask you to consider whether the model of care envisioned, in which physicians from various non-surgical specialties will receive training in the procedures, or will be expected to have trained personnel under their direct supervision, is a realistic model that can be implemented in addiction treatment practice.

4. We will ask the committee to comment on certain issues for which no information has been provided, addressing whether these are critical deficiencies in the application.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

Draft Topics for Discussion

1. Do the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence? In your discussion, please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose.

2. Has the Applicant adequately characterized the safety profile of Probuphine in this patient population? In your discussion, please comment on the Applicant's assessment of the safety aspect of Probuphine in general, as well as on safety concerns specific to the placement and removal of the implants.

3. Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for physicians who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure. Include in your deliberations any concerns related to the model of care, in which the the practitioner who inserts and/or removes the implants may not be the physician providing addiction treatment. Note that compliance with applicable laws and regulations will need to be considered in any proposal.

4. Please discuss whether the absence of any information on each of the following matters should be considered a critical deficiency in the application:
    a. the potential for removal of the implants by non-medical personnel for the purpose of diversion.
    b. the potential for long-term exposure to the components of the rods if an individual never has the implants removed.
    c. the potential for patients to require implantation into an arm which has received an implant previously in order to remain on treatment, which would necessitate identification of multiple implantation sites per arm, or use of previously-implanted sites.

5. Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application?

Probuphine Efficacy and Safety Background

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1 Executive Summary

Probuphine is a rod-shaped implant designed to provide sustained delivery of a therapeutic level of buprenorphine, a partial agonist at the μ-opiate receptor, for up to six months when 4 to 5 rods are implanted subdermally. Probuphine is intended as a maintenance treatment for opioid-dependent patients who have been initially titrated to a target dose using sublingual buprenorphine.

The Applicant has provided efficacy data from two placebo-controlled trials. While the study design (randomized, placebo-controlled, parallel group study of 6 months' duration) is not novel, some of the analytic approaches and concepts are. We will ask the Committee to consider whether the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence, particularly commenting on whether the dose appears to be adequate.

The Applicant's submission includes safety data from 262 unique patients who were treated with Probuphine, of whom 201 received one course of treatment (24 weeks) and 82 received a second course of treatment (a total of 48 weeks).

The overall safety experience is consistent with the known safety profile of buprenorphine. However, the product presents a novel safety concern due to the need for surgical implantation. It is similar in many respects to Norplant, an implantable, progestin-releasing contraceptive which is no longer marketed in the US.

Despite the fact that insertion and removal of Norplant were performed by providers trained in surgical procedures, the product's safety experience identified the potential for various implantation and removal-related complications, some of them with disabling consequences. Similar difficulties may be anticipated with Probuphine, perhaps further complicated by the population of both prescribers and patients. The Applicant has proposed a training program for providers, and a closed distribution system to ensure the product is implanted only by trained providers, to address these concerns. We will ask the committee to address whether these concerns, or any additional safety concerns, have been adequately addressed by the existing safety data, and adequately managed under the proposed Risk Evaluation and Mitigation Strategy (REMS) and whether the efficacy data are sufficient to outweigh the risks.

2 Introduction and Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[1]. A sublingual film formulation was approved in 2010. Approximately 10.7 million prescriptions from outpatient retail pharmacies were dispensed and approximately 1 million patients received a dispensed prescription for buprenorphine tablets or films during 2012.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ-receptor. Like methadone, buprenorphine's activity at the μ-receptor was expected to relieve patients' urge to use illicit opioids, but like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning.

Due to its partial agonist properties, the euphorigenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. This was expected to limit its attractiveness as a drug of abuse.

In addition, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use buprenorphine. This was predicted to serve as a further deterrent to abuse.

Finally, at sufficiently high doses, buprenorphine blocks full opioid agonists from achieving their full effects, further deterring abuse of these substances for buprenorphine-maintained patients.

Unfortunately, despite these features, buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in an increasing number of cases of accidental poisonings of young children. Therefore, a depot injection or an implantable product which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by young children, offers potential advantages. In addition, patients could not periodically discontinue use in order to allow the blocking effect to dissipate, so that they could experience the effects of their opioids of choice. Probuphine was developed to address these issues.

[1] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser NDA 20733). Naloxone is intended to further deter abuse by the intravenous route by precipitating withdrawal if the product is injected by persons dependent on full agonists.

The recommended dose of sublingual buprenorphine is in the range of 12 mg to 16 mg daily. Pharmacokinetic comparisons of Probuphine to sublingual buprenorphine demonstrate that the relative bioavailability of four Probuphine implants (320 mg total buprenorphine) based on the mean AUC_{0-24} values at steady state compared with sublingual buprenorphine (16 mg once daily) is 31.3%.

2.1 FDA-Approved Products for the Treatment of Opioid Dependence

Other approved products for the treatment of opioid dependence include buprenorphine sublingual formulations; methadone and levomethadyl acetate (LAAM, no longer marketed), both of which are full agonist treatments; and naltrexone (oral and depot formulations), an opioid antagonist. Treatment of addiction with methadone is limited to closely-regulated Opioid Treatment Programs (OTP), which may limit access to treatment. Buprenorphine treatment may be prescribed by specially-qualified physicians in office practice settings (see Appendix A).

2.2 Applicant's Rationale for Product Development

As noted above, buprenorphine sublingual products have been subject to diversion, and have been implicated in cases of accidental pediatric exposure. The Division agreed with the Applicant that Probuphine had the potential to meet an important public health need because implants would be more difficult to divert, and because young children are less likely to be accidentally exposed to an implanted rod than to sublingual formulations. This application has been accorded Priority Review status in recognition of this potential.

2.3 Clinical Development of Probuphine

There is no standard approach to clinical trial design and analysis for the treatment of opioid dependence. The other approved products were supported by a variety of studies with treatment as long as 40 weeks, and various analytic approaches were applied in evaluating the results. Titan conducted the development program for this indication with advice from the Agency on the trial design and analytic approach.

Titan expected that a single set of implants would be effective for as long as six months and designed their trials to allow for six months of observation time. The first clinical trial was designed to have an efficacy assessment at an earlier timepoint as the protocol-specified primary endpoint. In this way, if the efficacy throughout six months was not favorable, efficacy over the shorter time period could be evaluated without creating statistical concerns. Ultimately, however, Titan determined that the drug was effective for six months, and conducted the second trial accordingly. Therefore, although designated in the protocol as the primary endpoint, the analysis at the four-month time point will not be emphasized.

The choice of outcome measures was the subject of considerable discussion. The Division advised Titan that analyses focused on group means (such as mean percent of weeks abstinent) would be difficult to interpret, because they did not reflect the experience of individual patients, who might range from complete responders to complete non-responders. A significant effort was expended in trying to establish a definition of a treatment responder that could be applied to the studies; however, no definition of any drug use pattern, short of abstinence, could be identified that was supported by any specific data. Titan also cited literature reports in which group mean percent of clean urine tests were reported; however, because these group means incorporate both complete non-responders, partial responders, and good responders, the group mean value would not be an appropriate choice to define a responder. Therefore, rather than arbitrarily selecting a drug use pattern short of abstinence that would be considered successful, or agreeing *a priori* that complete abstinence would be an unreasonable expectation, Titan was encouraged to look at the full range of responder definitions, from complete abstinence to no abstinence, but to emphasize the effect of the drug on promoting abstinence or near-abstinence. This analysis is referred to by Titan as the "cumulative distribution function."

Recognizing that patients require some time for engagement in treatment, Titan was encouraged to also perform analyses in which a "grace period" was allowed during which drug use was not counted in the assessment of response.

Titan envisioned Probuphine as a product which could be provided to patients at the outset of their treatment—after just a few days of titration on a sublingual formulation. To support this indication, Titan was asked to provide evidence from replicated trials showing that Probuphine was appropriate treatment for patients who might not yet be stabilized on buprenorphine.

2.4 Safety Concerns Related to Surgically Implanted Drugs

The Agency's previous experience with surgically implanted products, specifically contraceptive implants, was used to identify potential concerns that could arise in the use of Probuphine, as well as upon the experience in the development program itself.

Implantable methods of contraception consist of devices that can be placed subcutaneously to provide long-acting, readily-reversible contraception. Four iterations of contraceptive implants have been approved for marketing in the United States, with each new generation featuring product designs aimed at improving tolerability. Norplant, the first generation of contraceptive implant, consisted of six levonorgestrel-containing capsules, was approved in 1990. Subsequent versions of implants include Jadelle (a two-capsule, levonorgestrel-containing implant), Implanon (a single-capsule, etonogestrel-containing implant), and Nexplanon (similar to Implanon, but is radio-opaque and detectable by X-ray). Currently, only Nexplanon is marketed in the U.S.

While implantable contraceptive methods are generally well-tolerated, procedure-related adverse events are notable for pain, infection, numbness, and scarring at the implant site.

Complications such as bleeding or hematoma have also been reported. Most significant safety concerns include injuries related to damage of the ulnar or medial cutaneous nerve, which have resulted in permanent disability.

Notably, implantable contraceptive products are inserted and removed by obstetrician/gynecologists, who are surgically trained specialists. Their medical offices are suitably equipped for the performance of minor surgical procedures; they have access to imaging modalities (such as ultrasound) for localizing implants that cannot be palpated, and to operating suites if a more extensive surgical procedure is required to manage a complication. In contrast, buprenorphine treatment is currently provided by physicians who may not have suitable training and may not practice in suitable environments to permit them to perform the implantation or removal procedures, or to manage complications.

The Applicant has described a model of care in which physicians who may or may not have surgical backgrounds would undergo a one-time training program to instruct them on the insertion and removal of the Probuphine rods. However, they note that perhaps one-third of patients would be treated under a divided care model, in which a different physician who had undergone the training program would perform the implantation procedure but would not take responsibility for the patient's addiction treatment. The patient would then be followed by a physician qualified to provide buprenorphine treatment of addiction, but who had not received the training on how to implant or remove the product, and potentially had no surgical background. In this scenario, follow-up care, and management of potential complications, would be provided by a physician who may not be equipped to manage them.

Drug utilization data indicate that 32% of prescriptions for buprenorphine/naloxone sublingual tablets are written by physicians whose specialty is identified as General Practitioner/Family Medicine/Doctor Of Osteopathy. While some of these individuals may perform minor surgical procedures, others may not be prepared to do so. Fully 22% of prescriptions are written by psychiatrists, whose training likely includes little in the way of surgical procedures, and whose office environments may be unsuitable for managing an implantation-site complication. Internists write 16% of prescriptions, while only a very small proportion of prescriptions are written by physicians whose specialties involve surgical training.

3 Clinical Pharmacology

The relative bioavailability of Probuphine (4 implants) compared to the recommended dose of sublingual buprenorphine tablets (16 mg/day) was evaluated in Study PRO-810, an open-label crossover study. Following an induction period, subjects received 16 mg/day SL buprenorphine for a minimum of five consecutive days after which time subjects received 4 Probuphine implants (80 mg buprenorphine/implant). The steady state C_{max} and AUC_{0-24} of buprenorphine following 16 mg sublingual buprenorphine were 10400±13400 pg/mL and 62666±36397 pg·hr/mL, respectively. The steady state C_{max} and

AUC_{0-24} on Day 28 after insertion of 4 Probuphine implants were 914±157 pg/mL and 19596±3372 pg·hr/mL, respectively. The relative bioavailability of Probuphine implants (320 mg total buprenorphine) based on the mean AUC_{0-24} values at steady state (Day 28) compared with SL buprenorphine (16 mg once daily) on Day-1 was 31.3%.

4 Non-Clinical Local Toxicity

Local tissue effects of Probuphine and Placebo (EVA only) implants were evaluated microscopically in dogs after subcutaneous exposures of 1 month and 10 months using standard testing protocols for medical devices.

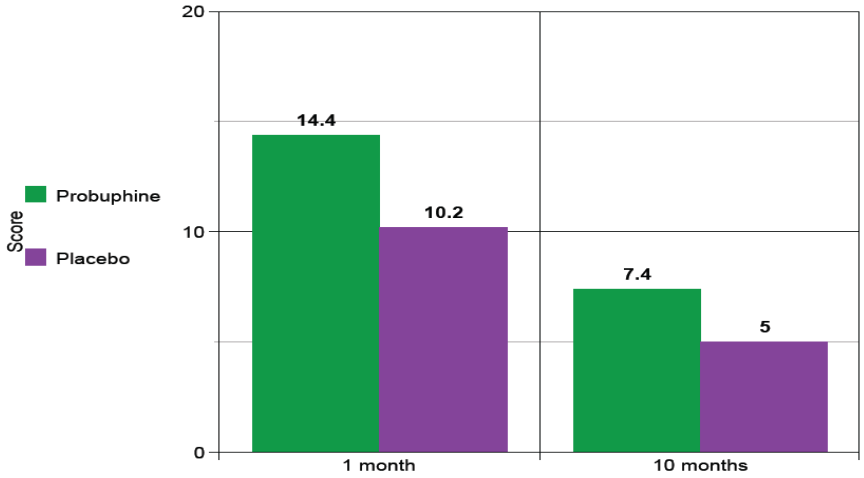
- Probuphine and Placebo were each moderately irritating after 1 month and slightly irritating after 10 months (see Figure 1).
- Predominant histological observations observed were generally more severe in Probuphine treated animals compared to Placebo animals.
- Severity of local toxicity decreased over time but was substantial during the early phase after implant insertion with the presence of buprenorphine in Probuphine causing increased local toxicity compared to Placebo (see Table 1)

Table 1. Severity[a] of Local Toxicity Based on Histological Observations in Dogs Treated with Probuphine or Placebo (EVA only) Implants for 1 or 10 months

Observation	Probuphine		Placebo	
	1 month	10 months	1 month	10 months
Increased fibrosis	1 to 4	1 to 2	1 to 3	1
Increased inflammatory cells				
Polymorphonuclear cells	1 to 3	0	1	0
Lymphocytes	1 to 3	1 to 2	1 to 3	0 to 1
Macrophages	1 to 4	0 to 3	1 to 3	0 to 1
Plasma cells	0 to 1	0 to 1	0	0 to 1

a - severity of fibrosis (0 - none, 1 – narrow band, 2 – moderately thick band, 3 – thick band, 4 – extensive band)
- severity of inflammatory cells (0 – none, 1 – rare, 2 – 5-10 per microscopic field, 3 – heavy infiltrate, 4 – packed)
Table prepared by reviewer from implant site histology data in study PRO-NTR-0215

Figure 1. **Individual Implant Local Toxicity Scores**[b]



b - Nonirritant (0.0-2.9), Slight Irritant (3.0-8.9)
Moderate Irritant (9.0-15.0), Severe Irritant (≥15.1)

Figure prepared by reviewer from implant site histology data in study PRO-NTR-0215

5 Review of Efficacy

Evidence of efficacy is provided from two placebo-controlled clinical trials, PRO-805 and PRO-806. Both were randomized, double-blind, parallel-group, multi-center studies involving efficacy ascertainment over 24 weeks after implantation of Probuphine or placebo implants. The study designs were essentially identical, except that PRO-806 also included a treatment group in which patients were treated with open-label sublingual buprenorphine.

5.1 Study Design and Endpoints

Both studies were randomized, double-blind, placebo-controlled, parallel group design. Eligible participants included patients 18 to 65 years of age who met DSM-IV criteria for current opioid dependence.

Patients were ineligible to participate if they had received treatment for opioid dependence in the previous 90 days, required opioid treatment of a current chronic pain condition, were considered candidates for short-term detoxification only, met criteria for dependence on other psychoactive substances (nicotine dependence permitted), or used illicit benzodiazepines. Medical reasons for exclusion included elevated hepatic enzymes, bilirubin, or creatinine; anticoagulant treatment; use of CYP3A4 inhibitors; a current AIDS diagnosis; or other medical or psychiatric conditions at investigator discretion.

Patients were to undergo initiation of buprenorphine treatment (induction) using sublingual tablets. In order to be randomized to treatment with Probuphine or placebo implant, patients had to meet the following criteria after the induction phase:

- Completed induction with sublingual buprenorphine to a dose of 12–16 mg/day as clinically appropriate within 10 days. Patients requiring <12 mg/day or >16 mg/day were ineligible.
- No significant withdrawal symptoms (defined as a score ≤ 12 on the Clinical Opiate Withdrawal Scale [COWS])
- No significant cravings for opioids (defined as a score ≤ 20-mm on the 100-mm Opioid Craving Visual Analog Scale [VAS])

Implantation occurred within 12 to 24 hours after the last dose of sublingual buprenorphine.

Patients were treated for 24 weeks on study. Following the randomization visit, there were approximately 88 scheduled visits: 16 study visits and 72 urine collection visits. Visits included assessments of safety (extent of exposure, adverse events [AEs], laboratory evaluations, vital signs, physical examination, electrocardiography [ECG]), concomitant medications) and efficacy (urine toxicology screening, quality of life, withdrawal symptoms and cravings, clinical global impressions [CGI]).

The protocols allowed for administration of supplemental sublingual buprenorphine during the study. Each dose of supplemental sublingual buprenorphine could only be obtained by patients at their clinic or pharmacy. Take-home sublingual buprenorphine was allowed for weekends, holidays, or other circumstances at the discretion of the investigator. Subjects in the open-label sublingual buprenorphine arm in Study PRO-806 could be provided up to seven days supply of sublingual buprenorphine at a time.

Criteria for supplemental sublingual buprenorphine were:
- Withdrawal symptoms scoring >12 on COWS
- Request for dose increase by subject that was considered appropriate by investigator
- Cravings >20 mm on the Opioid Craving VAS
- Other factors observed by the investigator

After the first two weeks, if a subject required supplemental sublingual buprenorphine dosing on 3 or more days per week for 2 consecutive weeks or on 8 or more days total over 4 consecutive weeks, the subject received an implant dose increase.

Any subject who requested, or who met one or more of the following criteria was withdrawn from the study:
- Subject non-compliance, defined as refusal or inability to adhere to the study protocol
    - missing 9 consecutive urine collections after the baseline visit
    - missing 6 consecutive counseling sessions after the baseline visit
    - refusal or inability to adhere to the study protocol, as determined by the principal investigator
- Evidence of implant removal or attempted implant removal
- Unacceptable or intolerable treatment-related AE

- Pregnancy
- Use of other treatments for opioid dependence
- Use of any investigational treatment
- Intercurrent illness or circumstances (e.g., incarceration ≥7 days) that, in the judgment of the investigator, affected assessments of clinical status to a significant extent
- Requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery
- Lost to follow-up
- Treatment failure, defined as
    - Requiring supplemental sublingual buprenorphine exceeding the following limits, after having received the optional 5th implant:
        - ≥3 days per week for 2 consecutive weeks
        - ≥8 days over 4 consecutive weeks at any time after the implant dose increase
    - Requiring >1 additional day per week of counseling for 4 consecutive weeks (i.e., >3 sessions per week during Weeks 1 through 12 and >2 sessions per week during Weeks 13 through 24)

(Note: results of urine testing for opioid use were not included in criteria for treatment failure.)

Any subject who met the above criteria was seen for an end of treatment visit (unless lost to follow-up), during which implants were removed and clinical evaluations performed.

The implantation procedure was performed by a health care provider who had received training from the sponsor on the technique. For Study PRO-805, the training consisted of a DVD and self-teaching materials. New training procedures and a new insertion device was developed after completion of Study 805, and for Study PRO-806, in-person training using an improved device was instituted. Implantation and removal procedures were typically provided by a specific "implanting physician" at each site. At some sites, the general management of the patient's addiction problem was handled by one individual (e.g., in the Department of Psychiatry) and arrangements were made for a physician with surgical experience (e.g., in the Department of Gynecology) to perform the implantation and removal procedures.

As discussed above, because of lack of consensus on what pattern of drug use short of abstinence should be deemed a successful outcome, but recognizing concern that patients might have occasional lapses, a primary endpoint capturing the full range of responses was used. The primary efficacy outcome for both studies was the cumulative distribution function (CDF) of the percent of urine samples negative for opioids. Study PRO-805 was the first Phase 3 trial in the clinical development program, and the CDFs were based on negative urine samples during Weeks 1 through 16. When Titan entered Phase 3 of the development program, the Applicant still had some uncertainty about the full duration of therapy with the implant. While Titan was operating under the theory that the implant provided buprenorphine for a total of six months, they acknowledged that it was conceivable that it only delivered active drug for four months. As such, when they

proceeded with the PRO-805 clinical trial, the strategy taken was to use a four-month window for the primary analysis and to subsequently also evaluate the six-month time period. The second Phase 3 study to replicate findings would be of six month duration if it worked for that whole time period during the initial study and a four-month duration if it worked for the lesser of the time periods. Since they judged that the implant lasts for six months, it renders the fourth month evaluations irrelevant.

In the final analyses, the primary endpoint of interest for both studies was the CDF of the percentage of negative urines for Weeks 1 – 24 with self-report imputation. This endpoint was based on urine toxicology findings. Urine samples were taken three times per week during the studies, and tested for opioids with the exception of buprenorphine, as well as other illicit drugs.[2] Positive urine samples underwent confirmatory testing. A sample found to be negative for opioids in the initial screen or confirmatory assay was defined as negative for purposes of data analysis.

Initially, the primary endpoint was to be adjudicated based on urine toxicology data alone. However, once preliminary data from the initial Phase 3 study and extension study were available, it appeared that patients in the Probuphine arm were reporting illicit drug use more frequently. Notably, this was all illicit drugs, not merely opioids. Given the likelihood of the self-report data to be factual when the patient admits to using illicit drugs, and the potential for false-negative urine samples, it seemed prudent to use all available sources of data to provide the most accurate picture of the clinical response with this product. Thus the opioid use self-report data (for illegal "street" opioids and prescription opioids for which the subject did not have a prescription) were used in the data analyses.

5.2 Population

A total of 331 patients were randomized to treatment with Probuphine (n = 222) or placebo (n = 109) in Studies PRO-805 and PRO-806.

- Study PRO-805 randomized 163 patients in a 2:1 ratio to either Probuphine or placebo. This study was conducted at 23 sites in the United States. The first

[2] Tested drugs for urine toxicology included the following:

1. Amphetamines: d-Amphetamine, d-Methamphetamine, Ecstasy
2. Barbiturates: Amobarbital, Butabarbital, Butalbital, Pentobarbital, Phenobarbital,Secobarbital
3. Benzodiazepines: Alprazolam + metabolites, Diazepam, Nitrazepam + metabolites, Flunitrazepam + metabolites, Oxazepam, Temazepam, Clonazepam + metabolites, N-desmethyldiazepam, Flurazepam + metabolites, Lorazepam
4. Δ9-tetrahydrocannabinol
5. Cocaine + metabolite benzoylecgonine
6. Methadone + metabolite EDDP (2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine
7. Methaqualone
8. ***Opiates: Codeine, Dihyrocodeine, Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone, Meperidine/Normeperidine, 6-Acetyl Morphine: 6-AM***
9. Phencyclidine
10. Phenothiazines: Chlorpromazine, Trifluoroperazine, Thioridazine/Mesoridazine metabolites
11. Propoxyphene, Norpropoxyphene
12. Tricyclic antideprepressants: Amitriptyline, Desipramine, Doxepin + metabolites, Imipramine, Nortriptyline

patient was enrolled on April 2, 2007, and the study was completed on June 19, 2008.

- Study PRO-806 randomized 301 patients in a 2:2:1 ratio to either Probuphine, open-label sublingual buprenorphine 12-16 mg per day, or placebo. The study was conducted at 20 sites in the United States. The first patient was enrolled on April 22, 2010, and the study was completed on May 12, 2011.

Selected demographic and baseline characteristics of the patients are shown in the Tables 2 and 3.

Table 2. **Characteristics of Patients in Study PRO-805**

Variable/Category	Probuphine n=108	Placebo n=55
Age (years)		
Mean (SE)	36 (1.1)	39 (1.6)
Range	19 – 62	20 – 61
Sex – n (%)		
Male	72 (67)	40 (73)
Female	36 (33)	15 (27)
Race – n (%)		
White	82 (76)	40 (73)
Black	14 (13)	6 (11)
Asian	-	1 (2)
American Indian or Alaskan Native	5 (5)	-
Native Hawaiian or Other Pacific Islander	1 (1)	-
Other	6 (6)	8 (15)
Ethnicity – n (%)		
Hispanic or Latino	12 (11)	12 (22)
Not Hispanic or Latino	96 (89)	43 (78)
Duration of Opioid Dependence (years) Study Initiation / Completion Dates: April 2, 2007 / June 19, 2008		
First Diagnosed in 2002-2007	78 (72)	40 (73)
First Diagnosed in 1996-2001	17 (16)	4 (7)
First Diagnosed in 1990-1995	8 (7)	6 (11)
First Diagnosed in 1984-1989	1 (1)	1 (2)
First Diagnosed in 1978-1983	1 (1)	3 (6)
First Diagnosed in 1972-1977	1 (1)	1 (2)
First Diagnosed in 1966-1971	2 (2)	-
Previously Treated for Substance Abuse/Dependence – n (%)		
Yes	73 (87)	36 (90)
No	11 (13)	4 (10)
Missing	24	15
Current Primary Opioid of Abuse		
Heroin	69 (64)	34 (62)
Prescription Opioid	39 (36)	21 (38)

Source: Adapted from Integrated Summary of Safety, Table 20 pp 72 – 73 & PRO-805 Final Study Report, Table 5 p. 55.

Table 3. Characteristics of Patients in Study PRO-806

Variable/Category	Probuphine n=114	Placebo n=54	OL SL BPN n=119
Age (years)			
Mean (SE)	36 (1.0)	35 (1.4)	35 (1.0)
Range	19 – 60	19 – 59	18 – 60
Sex – n (%)			
Male	72 (63)	31 (57)	72 (61)
Female	42 (37)	23 (43)	47 (40)
Race – n (%)			
White	95 (83)	45 (83)	97 (82)
Black	14 (12)	7 (13)	16 (13)
Asian	-	1 (2)	1 (1)
American Indian or Alaskan Native	3 (3)	-	-
Native Hawaiian or Other Pacific Islander	N/A	N/A	N/A
Other	2 (2)	1 (2)	5 (4)
Ethnicity – n (%)			
Hispanic or Latino	24 (21)	11 (20)	17 (14)
Not Hispanic or Latino	90 (79)	43 (80)	102 (86)
Duration of Opioid Dependence (years) Study Initiation / Completion Dates: Apr 22, 2010 / May 12, 2011			
First diagnosed in 2005-2010	85 (75)	42 (78)	82 (69)
First diagnosed in 1999-2004	13 (11)	6 (11)	16 (13)
First diagnosed in 1993-1998	6 (5)	4 (7)	7(6)
First diagnosed in 1987-1992	4 (4)	2 (4)	8 (7)
First diagnosed in 1981-1986	1 (1)	-	3 (3)
First diagnosed in 1975-1980	1 (1)	-	2 (2)
First diagnosed in 1969-1974	1 (1)	-	1 (1)
First diagnosed in 1963-1968	1 (1)	-	-
First diagnosed date missing	2 (2)	-	-
Previously Treated for Opioid Abuse – n (%)			
Yes	63 (55)	31 (57)	68 (57)
No	51 (45)	23 (43)	51 (43)
Current Primary Opioid of Abuse – n (%)			
Heroin	76 (67)	28 (52)	75 (63)
Prescription Opioid	38 (33)	26 (48)	43 (36)

Abbreviations: BPN=buprenorphine; OL=open-label; SE=standard error; SL = sublingual
Source: Adapted from Integrated Summary of Safety, Table 20 pp 72 – 73 & PRO-806 Final Study Report, Table 11-2 p. 89.

Patient disposition is illustrated below. Overall, 35% of the Probuphine-treated patients and 72% of the placebo-treated patients in the controlled trials did not complete the full 24 weeks of treatment. In the placebo arms, the most common reason for premature discontinuation was “treatment failure,” which, again, was defined as requiring more than the protocol-specified limit of supplemental sublingual buprenorphine. Continued use of illicit substances was not considered in the definition of treatment failure. Patient disposition for the individual studies is shown in Table 4 and includes both PRO-805 and PRO-806, and their respective open-label extensions, PRO-807 and PRO-811.

Table 4.Patient Disposition Phase 3 Efficacy Studies and Safety Extensions

Disposition	Double-Blind Studies					Open-Label Studies	
	Study PRO-805		Study PRO-806			Study PRO-807	Study PRO-811
	Probuphine N=108 n (%)	Placebo N=55 n (%)	Probuphine N=114 n (%)	Placebo N=54 n (%)	SL BPN N=119 n (%)	Probuphine N=62 n (%)	Probuphine N=85 n (%)
Subject Completed Study	71 (65.7)	17 (30.9)	73 (64.0)	14 (25.9)	76 (63.9)	46 (74.2)	67 (78.8)
Subject Withdrew Early	37 (34.3)	38 (69.1)	41 (36.0)	40 (74.1)	43 (36.1)	16 (25.8)	18 (21.2)
Most Common Reasons for Early Withdrawal							
Subject Request	8 (7.4)	9 (16.4)	5 (4.4)	9 (16.7)	4 (3.4)	5 (8.1)	7 (8.2)
Subject Non-Compliance	12 (11.1)	7 (12.7)	10 (8.8)	9 (16.7)	8 (6.7)	5 (8.1)	0 (0.0)
Treatment Failure	0 (0.0)	17 (30.9)	6 (5.3)	9 (16.7)	0 (0.0)	0 (0.0)	1 (1.2)
Unacceptable or intolerable treatment-related adverse event	4 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	2 (3.2)	0 (0.0)
Intercurrent illness or circumstance that affected assessments of clinical status or required discontinuation of drug or both	1 (0.9)	0 (0.0)	8 (7.0)	4 (7.4)	8 (6.7)	0 (0.0)	3 (3.5)
Lost to Follow-Up	10 (9.3)	4 (7.3)	9 (7.9)	3 (5.6)	17 (14.3)	4 (6.5)	6 (7.1)

0

Abbreviations BPN = buprenorphine; SL = sublingual
Note: Percent for each reason for early withdrawal is based on the total number of subjects in the population.
Source: Summary of Clinical Safety, Table 7, page 48.

5.3 Statistical Methodologies

The primary efficacy analysis compared the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids in the two treatment groups using a stratified Wilcoxon rank sum test with pooled site and gender as stratification variables.

The primary analysis for both studies was conducted on the intent-to-treat population, defined as all randomized patients who received an implant. The percentage of negative urines was derived for each patient by summing the total number of negative urine samples and dividing by all possible samples. For weeks 1-24, the denominator was 72. For some patients, the denominator was greater as they had unscheduled urine test results. Missing samples were considered positive. The following describes the categorization of samples:

- If a subject was withdrawn from the study, urine samples from that point onward were considered positive.
- If the urine sample provided by a subject was deemed non-authentic and an authentic sample could not be obtained, the sample was considered missing and therefore positive.
- If a valid urine sample was obtained from the subject (i.e., non-missing and valid collection on the eCRF), but was not included in the lab analysis (i.e., lost in transit or other reason), then the sample was considered non-missing, but not analyzed and was not considered a positive urine result.
- If urine sample data were missing for any other reason, the urine sample was considered positive.

In Study PRO-806, the percentage of negative urines also incorporated self-reported use. If a patient reported illicit use of opioids during a specific week, urine samples collected during that timeframe were considered positive even if a urine sample tested negative. This approach was utilized post-hoc in Study PRO-805.

It is noted that analyses which describe the percent of visits, samples, or weeks that are opioid-free cannot distinguish between patients who require some time to engage in treatment but ultimately attain and sustain abstinence, and patients who have an initial period of abstinence but relapse to regular drug use while still on-treatment. The former patient would be regarded as more successful than the latter. Moreover, if there were a number of patients in the latter category, this might suggest that the duration of effect of the implant had been over-estimated. Therefore, the data were examined using various "grace periods." In these analyses, drug use during the initial grace period is not included in the calculations. Patients who attained and sustained abstinence by the end of the grace period would be represented as fully abstinent. The data presented below show the results using no grace period, or using a grace period of four months (i.e., only drug use in the final two months "counts").

5.4 Results and Conclusions

Of note, all results presented were obtained by incorporating self-reported use. If a patient reported illicit use of opioids during a specific week, urine samples collected during that timeframe were considered positive even if a urine sample tested negative.

5.4.1 Analysis of Weeks 1-24

Figures 2 and 3 display the CDFs of percent negative urine samples for Weeks 1–24 with self-reported use incorporated. The figures differ from those presented by Titan which display the percent of patients who had a given proportion of negative samples *or fewer.* For this reason, Titan's cumulative distribution functions rise from zero at the left to 100% at the right. In our presentations, the graphs show the proportion of patients who provided a given proportion of negative samples *or better.* The curves therefore fall from 0% at the left to 100% at the right. For example in Study PRO-805, approximately 45% of the patients in the Probuphine group had at least 30% of urines samples clean. In comparison, approximately 27% of patients in the placebo group had at least 30% of urine samples clean.

Figure 2. Cumulative distribution of percent negative urines in Study PRO-805

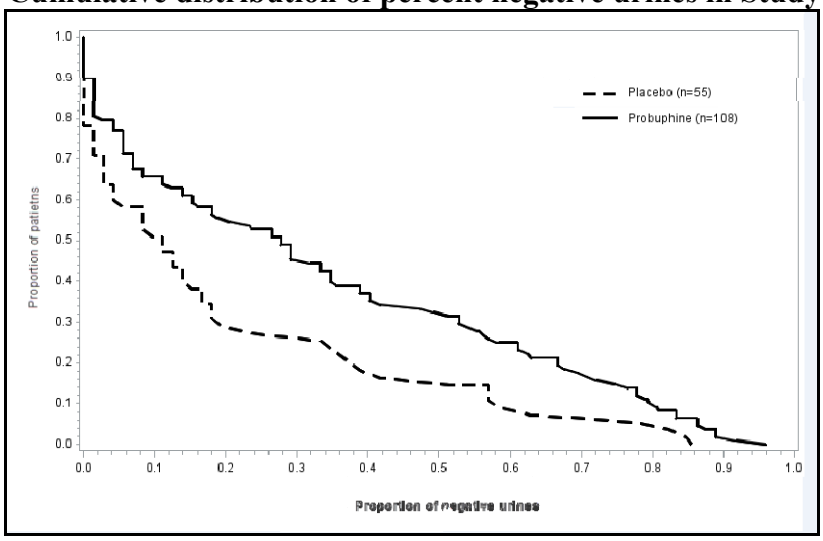
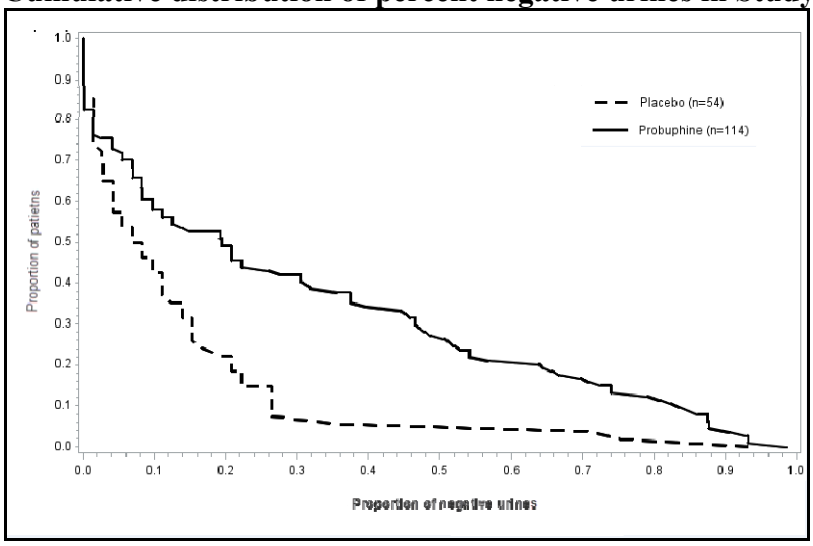


Figure 3. Cumulative distribution of percent negative urines in Study PRO-806



In both studies, the CDFs were statistically significantly different (p-values of 0.01 and <0.001 in the respective studies). In addition, there were more patients in the Probuphine arm that achieved at least 30%, 50%, or 80% negative urines. However, there were no patients in either study that achieved complete abstinence. This information is provided in tabular format in Table 5. For example, 7% of patients in the placebo group had at least 30% of urines clean compared to 42% of patients in the Probuphine group.

Table 5. Percent negative urines Weeks 1-24

Study	% Negative Urines	% of subjects	
		Placebo	Probuphine
PRO-805	≥ 30	27	45
	≥ 50	16	32
	≥ 75	7	15
	≥ 80	5	10
	≥ 85	2	6
	≥ 90	-	2
	≥ 95	-	1
	100	-	-
PRO-806	≥ 30	7	42
	≥ 50	6	27
	≥ 75	4	13
	≥ 80	2	12
	≥ 85	2	9
	≥ 90	2	4
	≥ 95	-	1
	100	-	-

To further examine the distribution of percent negative urine samples on a subject level, histograms were constructed and are shown in Figures 4 and 5. Each bar in the histogram represents the number of patients achieving various percentages of negative urine samples. For example in Study PRO-805, approximately 50% (27 patients) patients in the

placebo arm had between 0 and 10% of their urine samples negative compared with approximately 35% (37 patients) in the Probuphine arm.

Figure 4. Study PRO-805: Histogram of negative urines for Weeks 1−24

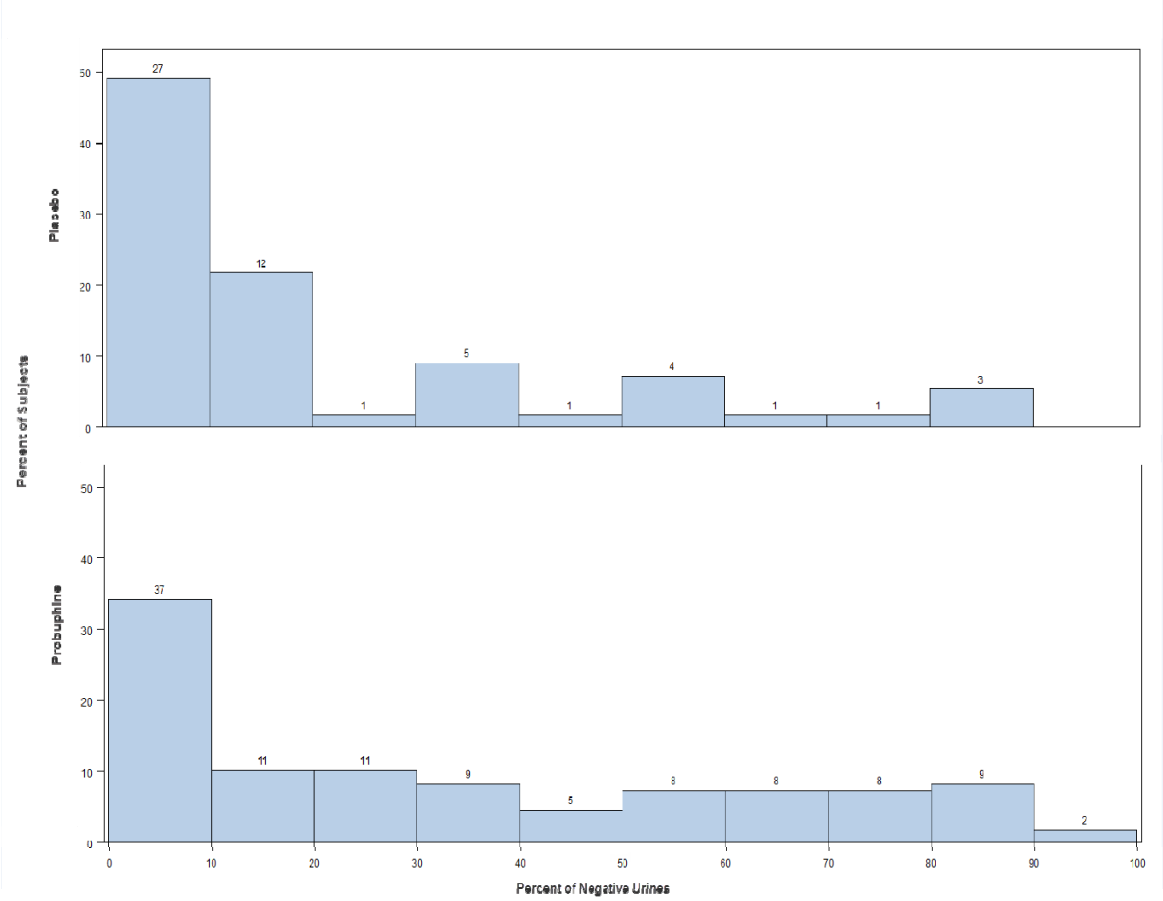
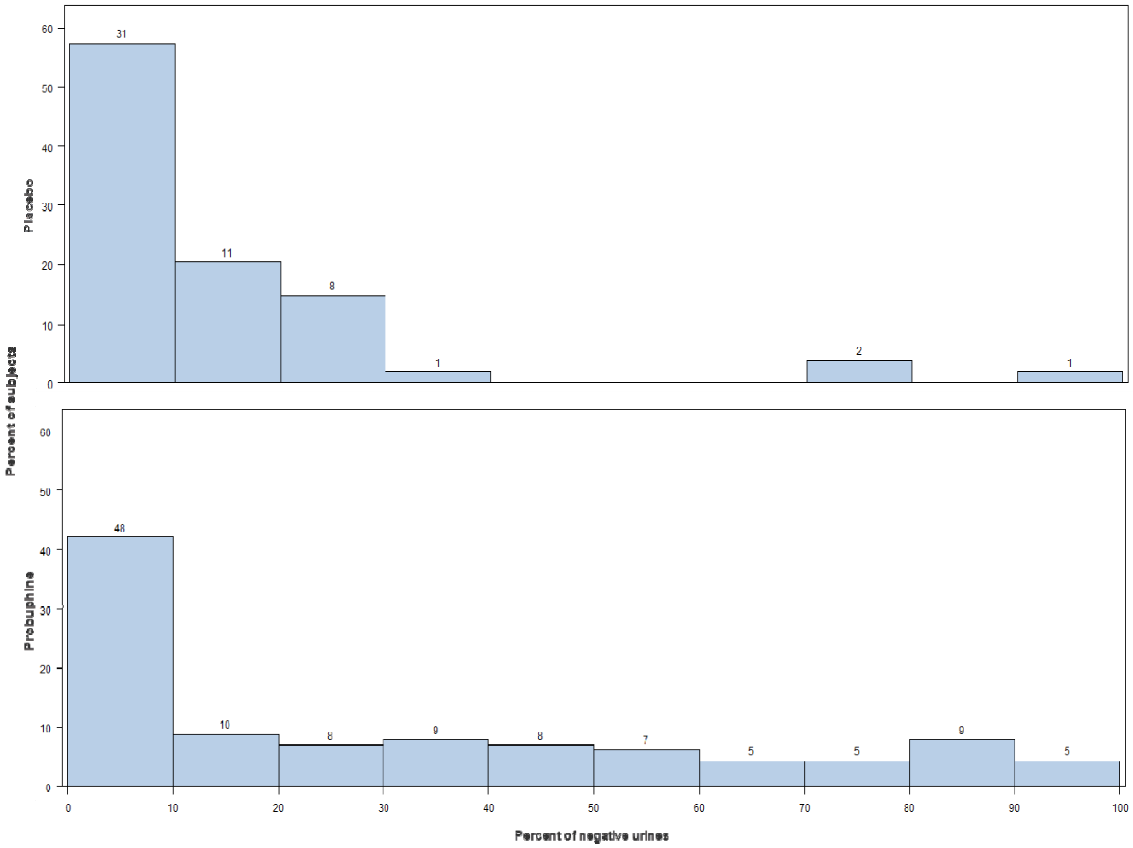


Figure 5. Study PRO-806: Histograms of negative urines for Weeks 1−24



5.4.2 Analysis Incorporating a Grace Period

We also evaluated the data allowing a grace period. We examined the last 8 weeks of treatment under the assumption that if the drug was not effective for 6 months, the CDFs for percent negative urines during Weeks 17–24 would look worse than the CDFs for Weeks 1–24. Conversely, if the curves looked better, it could suggest that given time, patients improve. CDFs of percent negative urines for the last 8 weeks of treatment (Weeks 17–24) are presented in Figures 6 and 7.

Figure 6. CDF of percent negative urines for Weeks 17-24 in Study PRO-805

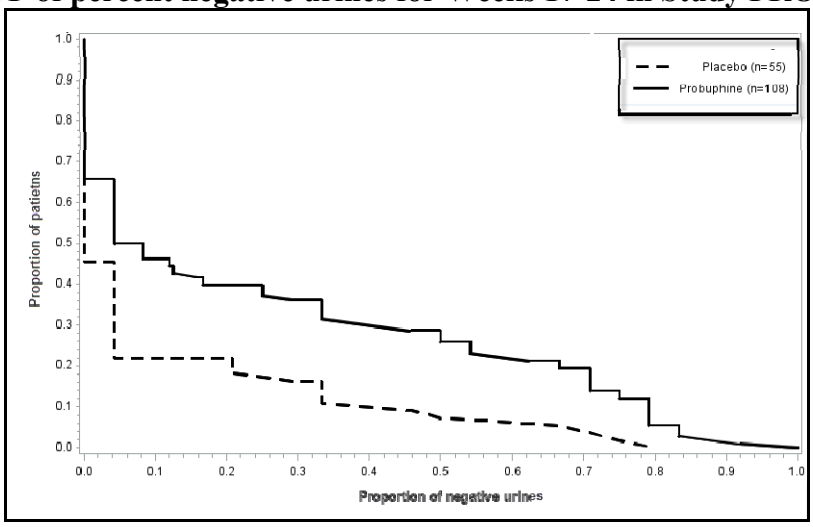
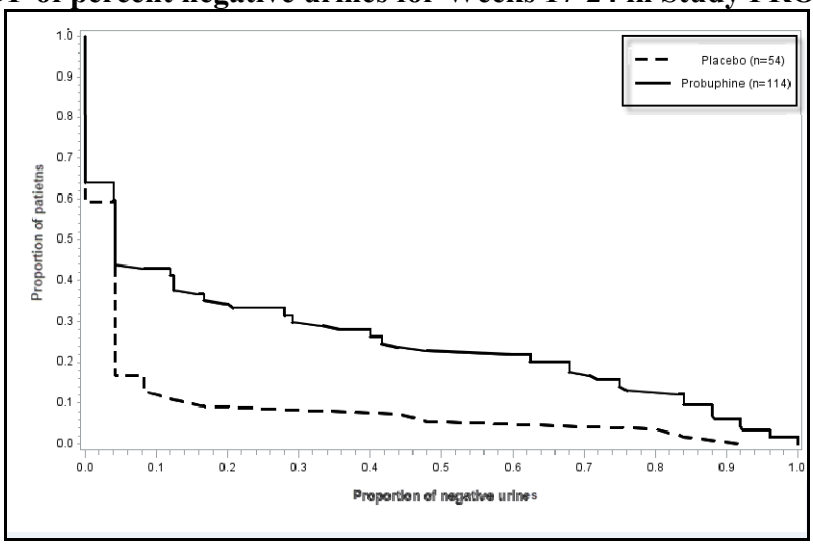


Figure 7. CDF of percent negative urines for Weeks 17-24 in Study PRO-806



This information is provided in tabular format in Table 6. For example, in Study PRO-806, 9% of patients in the placebo group had at least 30% of urine samples clean compared to 30% of patients in the Probuphine group.

Table 6. Percent negative urines Weeks 17-24

Study	% Negative Urines	% of subjects	
		Placebo	Probuphine
PRO-805	≥ 30	16	36
	≥ 50	9	29
	≥ 75	4	14
	≥ 80	2	6
	≥ 85	-	3
	≥ 90	-	2
	≥ 95	-	1
	100	-	1
PRO-806	≥ 30	9	30
	≥ 50	6	23
	≥ 75	6	16
	≥ 80	6	13
	≥ 85	2	10
	≥ 90	2	6
	≥ 95	-	4
	100	-	2

The data for Weeks 17-24 are also presented as histograms in Figures 8 and 9.

Figure 8. Histogram of percent negative urines for Weeks 17-24 in Study PRO-805

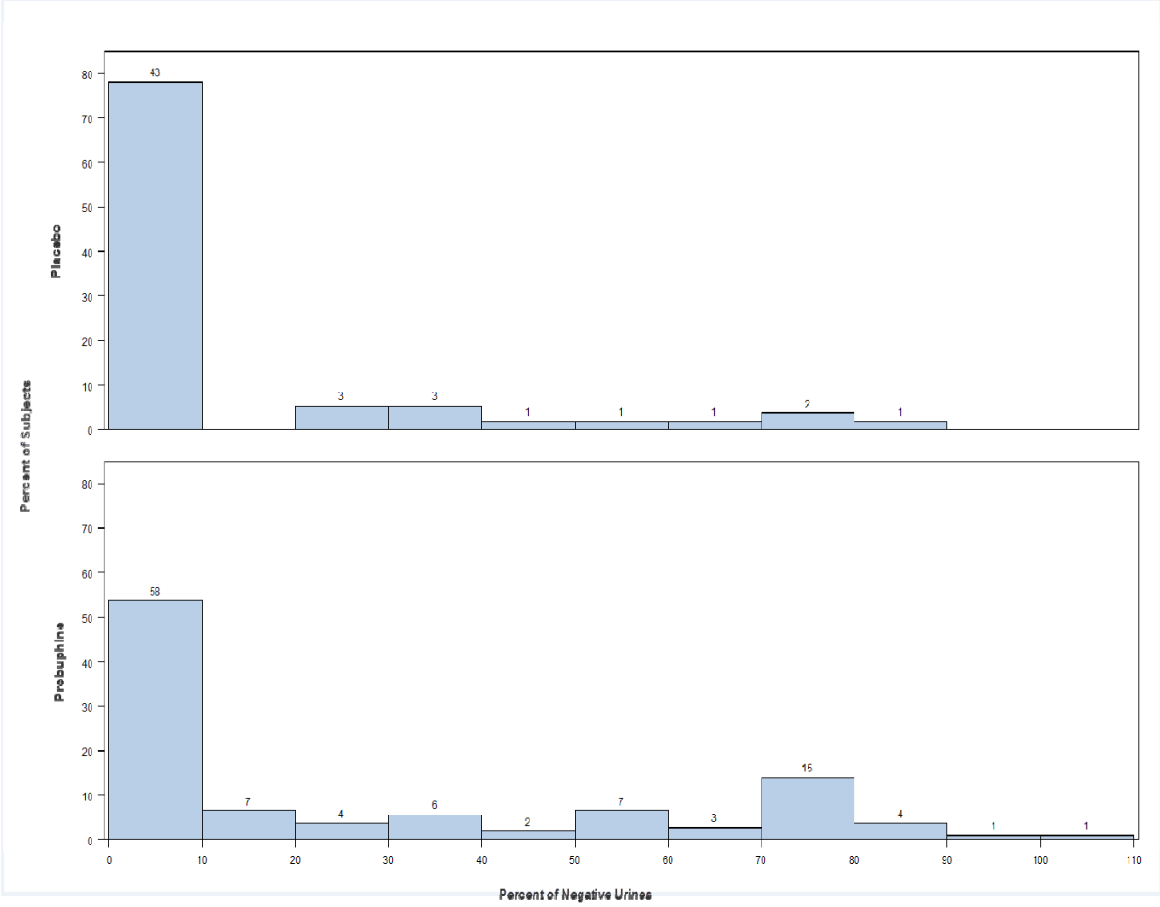
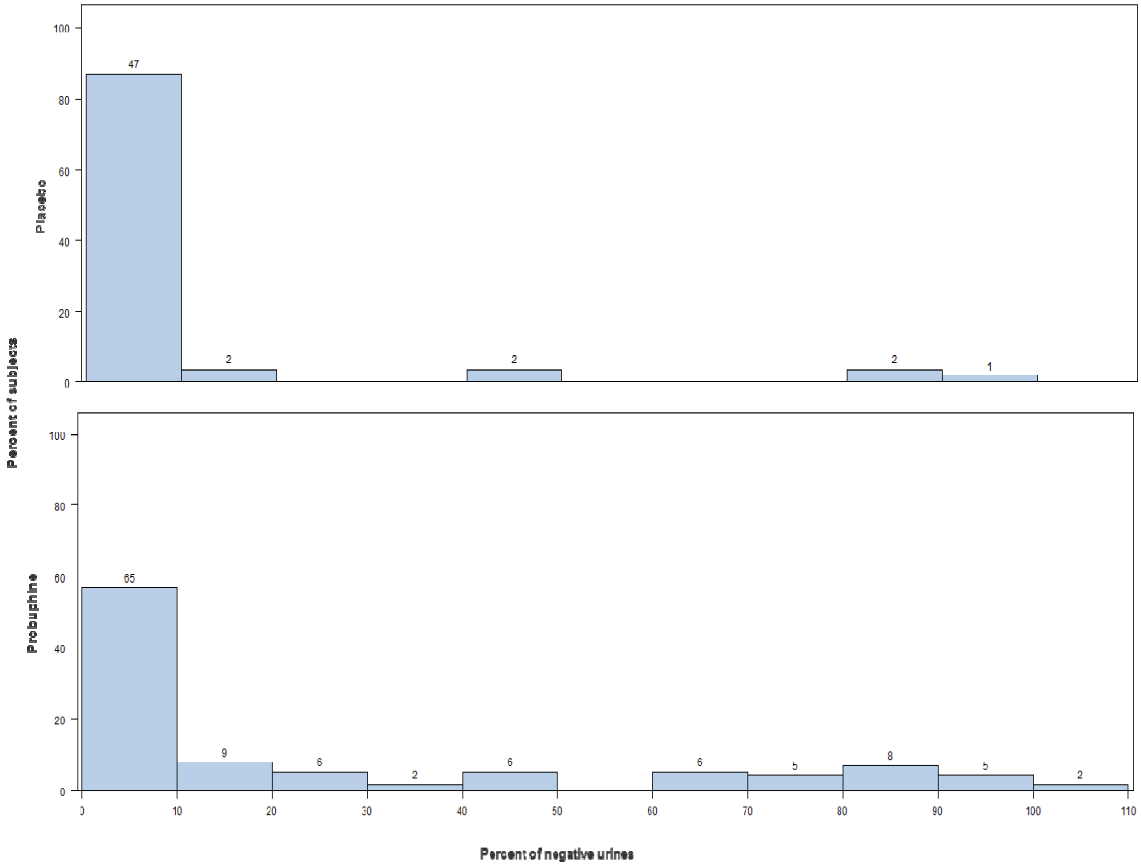


Figure 9. Histogram of percent negative urines for Weeks 17-24 in Study PRO-806



The results for the last 8 weeks of treatment were not conclusive. The distribution of negative urine screen for Weeks 17–24 did not differ from the distribution of the data for Weeks 1–24. It should be noted that there were three patients in the Probuphine arms that achieved complete abstinence when Weeks 1–16 were excluded from the analyses.

5.4.3 Analysis of Patients With Minimal Response

Analyses were also conducted exploring the percentage of patients that had all positive urine samples for Weeks 1 through 24. The results are shown in Table 7.

Table 7. All urines positive for Weeks 1 through 24

Study	Placebo	Probuphine
PRO-805	21%	10%
PRO-806	15%	18%

In Study PRO-805, there were more placebo patients having all positive urine samples than Probuphine-treated patients. This was not observed in Study PRO-806 where the

percentages were more similar. We further explored the data by investigating patients that had 95% or almost all of the urines positive. Results are shown in Table 8.

Table 8. 95% of urines positive for Weeks 1 through 24

Study	Placebo	Probuphine
PRO-805	40%	23%
PRO-806	43%	27%

More placebo patients had 95% or more of their urines positive versus Probuphine-treated patients.

5.4.4 Use of Supplemental Buprenorphine

Since patients were allowed to use supplemental sublingual buprenorphine (SL BPN), we examined time to first use of SL BPN. The proportion of patients that required SL BPN is shown in Table 9. The time-to-first use of SL BPN curves are shown in Figures 10 and 11 and suggest that a higher proportion of patients in the placebo arm used SL BPN early in the study. As depicted in the figures, the first dose of SL BPN for patients in the Probuphine arms occurred at various times throughout the study, and there were patients that needed SL BPN for the first time in the final month of treatment. This may imply that the dose is not adequate for some patients, even after steady state is reached, and that there may be patients for whom the dose does not last 24 weeks. The median time (in days) to first use of supplemental SL BPN are shown in Table 10.

Table 9. Percent of subjects requiring SL BPN

Study	Placebo	Probuphine
PRO-805	91%	64%
PRO-806	67%	39%

Additional details on the use of supplemental SL BPN are shown in tables in Appendix B.

Figure 10. Time to first use of SL BPN for Study PRO-805

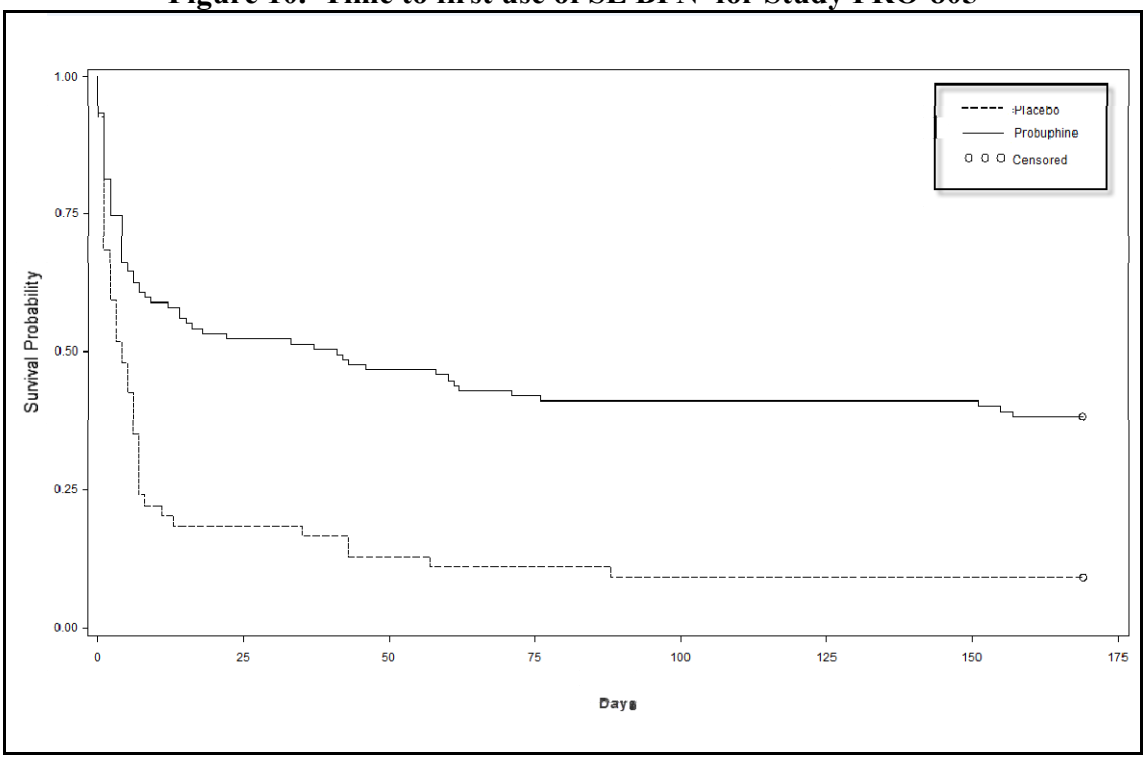


Figure 11. Time to first use of SL BPN for Study PRO-806

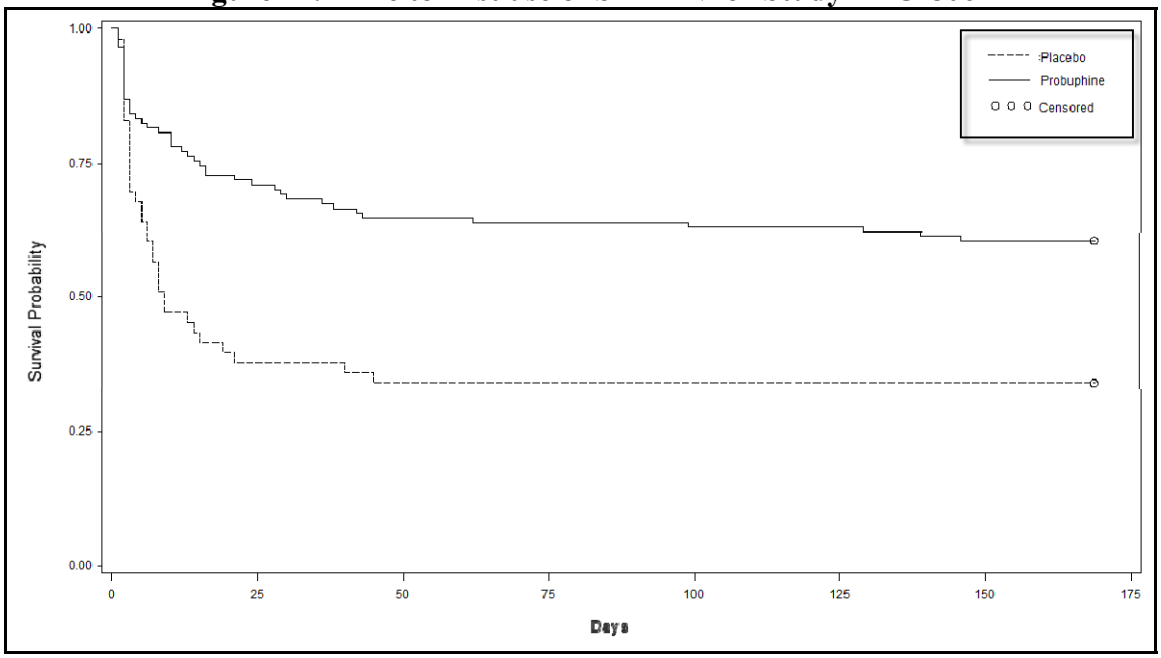


Table 10. Median times (days) to first use of supplemental sublingual buprenorphine

Study	Placebo	Probuphine
PRO-805	4	41
PRO-806	9	-

5.5 Discussion

The results above suggest that patients treated with Probuphine were more likely than patients treated with placebo to submit opioid-negative urine samples on more occasions, and were less likely to require supplemental sublingual buprenorphine for treatment of subjective symptoms of withdrawal or "craving." However, even after allowing four months for engagement in treatment, only three Probuphine-treated patients were fully abstinent from opioids. Approximately 8% provided negative samples for at least 80% of tests. (6% in Study PRO-805 and 10% in Study PRO-806).

At the other end of the spectrum, about a quarter of Probuphine-treated patients were unable to provide even as few as 4 opioid-negative urine samples over the course of six months.

While the placebo group had even more discouraging results, supporting the conclusion that Probuphine does have an effect on drug use, overall, the response was not what one might hope for, given that the product ensures compliance with medication for six months. It prompts speculation that the dose is simply not high enough. The dose of buprenorphine delivered by 4 Probuphine implants is less than a third of the dose delivered by 16 mg sublingual buprenorphine. It is possible that the dose is sufficient to provide some agonist effects but not to block the effects of exogenous opioids. Potentially, Probuphine could deliver just enough buprenorphine to allow patients to continue to use illicit opioids without experiencing withdrawal when they stop. This would explain the effects on retention in treatment, use of rescue buprenorphine, and scores on subjective scales of withdrawal, all of which seem to have been accomplished in many of the patients without yielding a compelling modification of the patients' drug-taking behaviors.

We will ask the committee to address whether the available efficacy data from these sources are sufficient to conclude that the drug is effective for the intended use. We will also ask whether the extent of efficacy demonstrated is sufficient to outweigh the risks, and whether further dose exploration should be required prior to approval.

6 Review of Safety

A total of 450 opioid-dependent patients were enrolled in the phase 3 studies, of whom 222 received Probuphine implants and 109 received placebo implants; an additional 119 were treated with sublingual buprenorphine and received no implants. A subset of these patients continued into open-label extensions providing data for longer-term exposure. Including patients receiving Probuphine in safety studies after completing the placebo arm, 262 patients received Probuphine in the efficacy and safety studies.

Note that, for the purposes of safety comparisons, patients identified as treated with "placebo," in most cases, received sublingual buprenorphine. Therefore, some common buprenorphine-associated adverse events may have occurred with similar frequency between the Probuphine arm and the placebo arm.

Table 11 represents the overall extent of exposure to Probuphine in the clinical trials. It should be noted that Studies PRO-805 and PRO-806 are the primary Phase 3 safety and efficacy studies, and each study had an open-label extension study into which patients could enroll upon completion of the primary studies. The extension studies are PRO-807 and PRO-811, respectively. Patients who participated only in the primary phase of the trial are represented only in the first six months of data for studies PRO-805 and PRO-806.

Table 11. Overall Exposure to Probuphine

Cumulative	< 1 month	≥ 1 month	≥ 2 months	≥ 3 months	≥ 4 months	≥ 5 months	≥ 6 months	≥ 7 months	≥ 8 months	≥ 9 months	≥ 10 months	≥ 11 months	≥ 12 months
TTP-400-02-01	12	12	12	12	12	12	12	0	0	0	0	0	0
PRO-805	108	102	99	96	87	81	74	0	0	0	0	0	0
PRO-806	114	112	109	108	103	99	92	0	0	0	0	0	0
PRO-807	12	12	12	11	11	10	10	57	52	51	51	50	47
PRO-810	9	8	0	0	0	0	0	0	0	0	0	0	0
PRO-811	28	26	24	23	21	21	20	74	73	72	70	68	67
Totals	**283**	**272**	**256**	**250**	**234**	**223**	**208**	**131**	**125**	**123**	**121**	**118**	**114**

Note: Study drug exposure is calculated as the date of implant removal minus the date on implant insertion plus one. If the removal date is missing, the study discontinuation date from the CRF is used. For PRO-805, PRO-806, PRO-807 and PRO-811, subjects that complete their respective study are assigned six months of exposure in that study. Open label studies display total exposure including exposure from double blind period. Subjects with more than 28 weeks of exposure in a given study are recorded as 28 weeks.

Note: A month is defined as 365.25/12 days.

Table 12 displays the demographic characteristics of the participants in the controlled trials.

Table 12.

Demographic Parameter	**Probuphine (N=222)**	**Placebo (N=109)**	**Total (N=331)**
Sex			
Male	144 (65%)	71 (65%)	215 (65%)
Female	78 (35.%)	38 (35%)	116 (35%)
Race			
White	177 (80%)	85 (78%)	262 (79%)
Black	28 (13%)	13 (12%)	41 (12%)
Asian	0 (0%)	2 (2%)	2 (1%)
American Indian or Alaskan Native	8 (4%)	0 (0%)	8 (2%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0 (0%)	1 (0.3%)
Other	8 (4%)	9 (8.%)	17 (5%)
Ethnicity			
Hispanic or Latino	36 (16%)	23 (21%)	59 (18%)
Not Hispanic or Latino	186 (84%)	86 (79%)	272 (82%)
Age (years)			
Median	34	35	35
Mean (SE)	36.1 (0.74)	37.2 (1.07)	36.5 (0.61)
CI (mean)	(34.6, 37.5)	(35.1, 39.4)	(35.3, 37.7)
Range (minimum-maximum)	(19, 62)	(19, 61)	(19, 62)
Age group			
18-35 years	115 (52%)	55 (51%)	170 (51%)
36-65 years	107 (48%)	54 (50%)	161 (49%)
Primary opioid of abuse			
Heroin	145 (65%)	62 (57%)	207 (63%)
Prescription opioid pain reliever	77 (35%)	47 (43%)	124 (38%)
Opioid abuse treatment history			
Yes	144 (65%)	69 (63%)	213 (64%)
No	78 (35%)	39 (36%)	117 (35%)
Missing	0 (0%)	1 (1%)	1 (0.3%)
BMI(kg/m^2)			
Median (n)[a]	24.82 (218)	23.992 (107)	24.536 (325)
Mean (SE)	25.781 (0.3658)	25.729 (0.5576)	25.764 (0.3059)
CI (mean)	(25.060, 26.502)	(24.623, 26.834)	(25.162, 26.366)

Demographic Parameter	Probuphine (N=222)	Placebo (N=109)	Total (N=331)
Range (minimum-maximum)	(17.59, 67.04)	(17.97, 54.65)	(17.59, 67.04)
≤25 (kg/m2)	114 (51%)	62 (57%)	176 (53%)
>25 (kg/m2)	108 (49%)	47 (43%)	155 (47%)

BMI = body mass index; CI = confidence interval; SE = standard error

[a] Height and/or weight data were not available for all patients.

Source: Integrated Summary of Efficacy, pp. 43 – 44

6.1 Major Safety Results

6.1.1 Deaths

There were no deaths in Probuphine-treated patients. One death occurred in the sublingual buprenorphine arm, attributed to heroin overdose.

6.1.2 Serious Adverse Events

Serious adverse events were reported in 8 (4%) of the patients randomized to Probuphine in the controlled trials, 7 (6%) of the patients randomized to placebo, and 6 (5%) of the patients randomized to sublingual buprenorphine. Additionally, 3 SAEs were reported in patients continuing on Probuphine in the open-label extensions and in one patient who completed placebo treatment in the controlled studies and was started on Probuphine in the open-label extension. Several of the events were of an infectious nature, including abscesses potentially related to intravenous drug use. Depression and suicidal ideation were also reported. One SAE related to the implant site was reported in a patient who received a placebo implant. However, because the risks of implantation are likely to be related to the procedure, and not to the drug, this event is of concern even in a placebo-treated patient. Table 13 briefly lists the types of events reported.

Table 13. Serious Adverse Events

Pooled DB Studies – PRO805 & PRO-806		
Probuphine (4%)	**Placebo (6%)**	**SL BPN (5%)**
1. Hypotension (sepsis, BP meds) 2. COPD exacerbation & PE 3. Pneumococcal pneumonia 4. Pneumonia 5. Umbilical hernia, obstructive 6. Tooth abscess 7. Second degree burns 8. Breast cancer	1. Respiratory Failure (heroin withdrawal; agitation → intubation) 2. Suicidal Ideation 3. Tylenol overdose (per pt 50 500-mg pills) 4. Pneumonia; Explant Site Cellulitis (805) 5. Limb abscess (not implant site) 6. Gastroenteritis 7. Relapse	1. Major depression 2. Pyrexia (infxn) 3. Angina pectoris 4. Pulmonary embolism 5. Rib fracture 6. Spontaneous abortion
Pooled OL Extension Studies – PRO-807 & PRO-811		
Probuphine → Probuphine	**Placebo → Probuphine**	
1. CAD, worsening 2. Cellulitis antecubital fossa (methamphetamine IV) 3. Suicidal ideation	1. Pneumonia (pneumonia in primary study also)	
Clinical Pharmacology Study PRO-810		
1. pancreatic cyst x 2, nausea		

6.1.3 Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation were uncommon in both active- and placebo-treated patients. Notably, the most common type of event leading to discontinuation involved problems at the implant site. However, all of these occurred in Study PRO-805 and its extension, Study PRO-807. The procedures used for implant/removal in those studies differed from those used in PRO-806 and PRO-811. Table 14 illustrates events leading to discontinuation, noting the study number in which the event was reported.

Table 14. Adverse events leading to patient discontinuation

Pooled Double-Blind Studies – PRO-805 & PRO-806		
Probuphine (3%)	**Placebo (2%)**	**SL BPN (4%)**
1. Implant Site Pain/Infection (805) 2. Implant Site Pain/Infection (805) 3. Implant Site Pain (805) 4. Hepatic Enzyme increases (805) 5. LFT abnormal (806) 6. Breast Cancer (806)	1. Tylenol Overdose (806) 2. Hepatitis C (806)	1. ALT/AST increased (806) 2. Weight decreased (806) 3. Neck pain (806) 4. Sinus tachycardia (806) 5. Drug dependence (806)
Pooled OL Extension Studies – PRO-807 & PRO-811		
1. Implant Site Hemorrhage, Infection, Edema & Erythema (807) – Probuphine 2. Implant Site Infection (807) – Probuphine 3. ALT increased (811) Probuphine → SL BPN induction		
Clinical Pharmacology Study PRO-810		
1. Adverse dropout in BA Study (810) – pancreatic cyst		

6.1.4 Common Adverse Events

The adverse event profile of sublingual buprenorphine has been previously characterized in the safety database for buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets. The adverse event tables from the approved labeling are shown in Appendix A.

Table 15 illustrates the common adverse events in the pooled double-blind studies in the Probuphine development program, excluding those events related to the implantation site or procedure. (These events are discussed separately in Section 6.1.5.1.)

Table 15. Common Non-Implant Site Treatment-Emergent Adverse Events (≥ 5% in the Probuphine group or Placebo/SL BPN group) in the Pooled Double-Blind Studies, PRO-805 and PRO-806

System Organ Class MedDRA Preferred Term	PROBUPHINE N=222 n (%)	Placebo/SL BPN N=228 n (%)
Any Non-Implant Site TEAE	158 (71.2)	158 (69.3)
Infections and Infestations	89 (40.1%)	89 (39.0%)
Upper respiratory tract infection	24 (10.8)	20 (8.8)
Nasopharyngitis	20 (9.0)	18 (7.9)
Gastrointestinal Disorders	67 (30.2%)	54 (23.7%)
Nausea	19 (8.6)	13 (5.7)
Constipation	16 (7.2)	9 (3.9)
Vomiting	15 (6.8)	10 (4.4)
Toothache	14 (6.3)	7 (3.1)
Diarrhea	8 (3.6)	12 (5.3)
Psychiatric Disorders	51 (23.0%)	56 (24.6%)
Insomnia	26 (11.7)	34 (14.9)
Anxiety	12 (5.4)	14 (6.1)
Depression	14 (6.3)	8 (3.5)
Nervous System Disorders	52 (23.4%)	47 (20.6%)
Headache	33 (14.9)	29 (12.7)
Dizziness	11 (5.0)	6 (2.6)
Musculoskeletal and Connective Tissue Disorders	37 (16.7%)	35 (15.4%)
Back pain	17 (7.7)	12 (5.3)
Respiratory, Thoracic and Mediastinal Disorders	35 (15.8%)	20 (8.8%)
Oropharyngeal pain	13 (5.9)	8 (3.5)

Source: Adapted from Integrated Summary of Safety Tables, Table 8.2.4.1.1: Summary of Non-Implant Site Adverse Events by System Organ Class and Preferred Term Safety Population Double Blind Studies: PRO-805 and PRO-806, pages 1128 – 1144

6.1.5 AEs of Special Interest

Based on mechanism of action, and on safety concerns identified during the original NDA review and in postmarketing safety experience, the safety database was evaluated for the following adverse events:

1. Implantation site reactions and complications of insertion or removal
2. Hepatic effects
3. QT prolongation

6.1.5.1 Implantation site reactions and complications of insertion or removal

During the Probuphine clinical trials, the implant site was to be evaluated at each clinic visit. The implant site was to be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. The implant site was also to be examined for evidence of removal or attempted removal of the implants. Treatment-emergent adverse events (TEAEs) related to the implant site were collected in two ways in the phase 3 double-blind and open-label studies. In Study PRO-805 and Study PRO-807, the case report form (CRF) presented a check list of 6 possible implant site TEAEs, as well as "Other implant site TEAE" and "non-implant site TEAEs." Only "Other implant site TEAEs" and "non-implant site TEAEs had free-text recorded. In Study PRO-806 and Study PRO-811, there was a CRF check box to designate TEAEs as implant site related. All TEAEs had free text descriptions that were coded; the determination of implant/non-implant status was based on the CRF check box (as summarized in ISS Section 2.1.4.6.1. Collection of Implant Site Data by Study, p. 37).

Tables 16 to 19 illustrate the number of patients experiencing various implant-site related adverse events associated with insertion. Some of these events (erythema, itching) are to be expected. However, others, such as hematoma or hemorrhage, represent complications of a more concerning nature. Drawing from the experience with other implantable drug products, certain implant-site related complications may require intervention, potentially in an operating room. In the tables below, a column representing all patients (Probuphine or placebo) is included because the procedures were the same for all patients. Although animal studies indicate that buprenorphine does have some irritant properties, the risks of the procedure itself are likely similar even when a placebo implant is inserted.

Studies PRO-805 and PRO-807 were conducted under the original procedures for training and using the original insertion device. PRO-806 and PRO-811 used the modified procedures and equipment.

Table 16. Common Implant Site AEs reported in ≥ 2 patients in PRO-805

Implant Site TEAE from CRF or Pre-Specified List	Probuphine N=108	Placebo N=55	Total N=163
Any Implant Site TEAE per CRF	62 (57)	25 (46)	87 (53)
Erythema	27 (25)	12 (22)	39 (24)
Itching	27 (25)	8 (15)	35 (21)
Pain	24 (22)	6 (11)	30 (18)
Edema	14 (13)	5 (9)	19 (12)
Bleeding	13 (12)	7 (13)	20 (12)
Infection	4 (4)	1 (2)	5 (3)
Other Implant Site TEAE	27 (5)	15 (27)	42 (26)
Scar	10 (9)	7 (13)	17 (10)
Bruising	6 (6)	8 (15)	14 (9)
Reaction	6 (6)	0 (0)	6 (4)
Hemorrhage	4 (4)	1 (2)	5 (3)
Pain	4 (4)	2 (4)	6 (4)
Impaired healing	3 (3)	0 (0)	3 (2)
Erythema	3 (3)	0 (0)	3 (2)
Hematoma	2 (2)	1 (2)	3 (2)
Irritation	2 (2)	0 (0)	2 (1)
Pruritis	1 (1)	1 (2)	2 (1)
Rash	1 (1)	1 (2)	2 (1)

Source: Adapted from Table 37: Implant Site Treatment-Emergent Adverse Events by Classification in Study PRO-805, Summary of Clinical Safety, p. 112.

Table 17. Common Implant Site AEs reported in ≥ 5% patients in PRO-807

Implant Site TEAE – n (%)	Probuphine N = 85
Any Implant Site TEAE	28 (45)
Implant site erythema	16 (26)
Implant site itching	12 (19)
Implant site pain	12 (19)
Implant site bleeding	10 (16)
Implant site edema	8 (13)
Other implant site TEAEs [a]	
General Disorders and Administrative Site Conditions	13 (21)
Implant site bruising	6 (10)
Implant site hemorrhage	4 (7)

TEAE = treatment-emergent adverse events

[a] Other implant site TEAEs were coded into system organ class and PT using the Medical Dictionary for Regulatory Activities, Version 10.0. Patients were counted at most 1 time per system organ class and 1 time per PT.

Source: Summary of Clinical Safety, Table 41, p. 121

Table 18. Common Implant Site AEs reported in ≥ 2 patients in PRO-806

Preferred Term	Probuphine N=114	Placebo N=54	Total N=168
Any Implant Site TEAEs	31 (27)	14 (26)	45 (27)
Erythema	4 (4)	0 (0)	4 (2)
Hematoma	8 (7)	6 (11)	14 (8)
Hemorrhage	2 (2)	2 (4)	4 (2)
Edema	2 (2)	0 (0)	2 (1)
Pain	6 (5)	5 (9)	11 (7)
Pruritis	5 (4)	0 (0)	5 (3)
Swelling	2 (2)	0 (0)	2 (1)
Procedural pain	4 (4)	0 (0)	4 (2)
Procedural site reaction	3 (3)	1 (2)	4 (2)
Ecchymosis	2 (2)	0 (0)	2 (1)

Source: Adapted from Table 39: Implant Site Treatment-Emergent Adverse Events in >1 Subject by Preferred Term in Study PRO-806, Summary of Clinical Safety, p. 117

Table 19. Implant Site AEs reported in ≥ 1 patient in PRO-811

Implant Site TEAE – n (%)	Probuphine N = 85
Any Implant Site TEAE	12 (14)
Implant site erythema	1 (1)
Implant site haematoma	2 (2)
Implant site haemorrhage	3 (4)
Implant site pruritus	1 (1)
Implant site rash	2 (2)
Implant site reaction	1 (1)
Cellulitis	1 (1)
Implant site abscess	1 (1)
Implant site infection	1 (1)
Subcutaneous abscess	1 (1)

Source: Adapted from Table 14.3.1.2: Summary of All Implant Site Adverse Events by System Organ Class and Preferred Term, Safety Population, PRO-811 Study Report, p. 541

These tabulations show that the overall rate of implant-site related AEs was reduced from roughly half of all patients receiving implants to about a quarter after implementation of the new insertion device and training procedures. However, for reference, the labeling for Nexplanon, an implantable contraceptive, indicates that implant site reactions were noted in 8.6% of patients, including 3.3% with erythema, 3% hematoma, 3% bruising, 1% pain and 0.7% swelling. Nexplanon requires only one implant, and the insertion device has been developed for one-handed insertion. Moreover, it is typically placed by clinicians who have surgical training and are experienced in the placement of implantable contraceptives. By contrast, the Probuphine implants require the insertion of four rods into one incision, and the procedures were performed by physicians with a variety of medical backgrounds, including some with little or no surgical training. About half of the

insertion procedures were performed by physicians whose specialty training was related to surgery.

Adverse events associated with removal of the implants were reported in 23% of removals in Study PRO-805 and in 13% of removals in Study PRO-806. In Study PRO-805, under half of the removals were performed by physicians with surgical specialties and in Study PRO-806, 66% of the removals were performed by physicians with surgical specialties.

Ultrasound location of implants was required in some cases. The implants are not radio-opaque and cannot be located with x-ray.

- PRO-805: 33 U/S performed – 9 instances for 4 patients; 10 instances for 1 site that randomized 13 patients
- PRO-806 – 2 U/S performed before and 2 after removal procedure
- PRO-807 – 5 U/S performed; 2 patients had > 1 record
- PRO-811 – 5 U/S performed; 2 patients had a U/S performed before and after

6.1.5.1.1 Complications

Several patients—all Probuphine-treated—experienced complications such as expulsion and extrusion of implants. These are described below.

Implant Expulsions – all in Probuphine arm

- 002-019 – 20M presented to clinic 1 wk post Wk4 visit, pulled out 3 Probuphine implants at visit, 4th removed by a study MD. Pt. admitted to attempting to remove protruding implants at home, prior to presenting to clinic, and d/ced from study. (PRO-805)

- 608-025 – 36M 1 implant had "popped through" while pt showered ~1 mo. after implantation. Pt. brought in implant. Had infection at implant site. Was to have replacement implant, but infection continued. Arrested for probation violation, addl implant came out at that time that he threw away. Infection resolved, remaining 2 implants removed, U/S performed to confirm. (PRO-806)

- 021-001 – 51F In PRO-805, protruding implant ~ 1 mo after implantation and implant replacement, 2 broken implants ~ 2 mos after implantation replaced with 2 new implants. All 5 implants removed without incident at end of study. In PRO-807, Probuphine implants replaced on 3 separate occasions due to various implant site TEAEs. (PRO-807)

Implant Extrusions – all in Probuphine arm

- 006-003, 40M had "implant fragment surfacing" ~ 7 mos after insertion. Pt recovered, no action taken regarding implant. (PRO-805)

- 021-001, 51F, as above (PRO-805)

- 027-013 27M 2 implants "extruding from incision site" ~3 wks after insertion, and 2 new implants inserted. Multiple implant site reactions during the timeframe. (PRO-805)

- 004-001, 27F, "implant site extrusion of 2 implants," ~2.5 mos after insertion. No action taken, and subject recovered (PRO-807)

6.1.5.2 Hepatic Effects

Buprenorphine has been associated with hepatitis and other hepatic events. The *Warnings and Precautions* section of current labeling for sublingual buprenorphine (as Suboxone) includes safety labeling regarding hepatitis and hepatic events as follows:

> **5.6 Hepatitis, Hepatic Events**
> Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual tablet may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

Hepatitis and hepatic events are considered part of the known safety profile of buprenorphine. In evaluating the hepatic safety of Probuphine, the objective was to determine if the hepatic safety findings from the Probuphine clinical trial database were consistent with the known safety profile of buprenorphine, and to identify new safety concerns, if any, with buprenorphine or buprenorphine in this new formulation. To facilitate this effort, the Applicant was advised to search the pooled safety database for "Hy's Law"[3] cases, which are considered indicative of potential drug-induced liver injury. The Applicant used the following liver function test criteria to identify possible Hy's Law cases: ALT >3X ULN (upper limit of normal) or AST >3X ULN, and Total bilirubin >2X ULN or >50% elevated over baseline. In so doing, the Applicant identified Hy's Law cases in the Probuphine arm (n=3, 1.4%) and the combined placebo/sublingual buprenorphine arm (n=6, 2.6%) of the pooled double-blind studies. An additional 5 patients on Probuphine in the open-label extension studies were identified as meeting Hy's Law criteria.

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[3] Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Excerpt from Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

The laboratory conventions used most commonly for identifying Hy's Law cases are AST or ALT elevations > 3xULN along with total bilirubin elevations ≥ 2xULN. On review of the cases identified by the Applicant as meeting Hy's Law criteria, the majority met the definition due to transaminitis in the setting of bilirubin elevations that were more than 50% higher than the baseline values, although still within normal limits. Although these cases all involved transaminase elevations, and sometimes marked transamanitis, there were no cases identified in which there was a concurrent biliribun elevation to ≥ 2xULN. In two cases where the bilirubin approached a two-fold ULN elevation, other plausible alternative explanations for the pattern of LFT abnormalities were identified, namely a Tylenol overdose a few days prior (one time dose of 25,000 mg) in one case, and a new diagnosis of Hep C in the other. In one other case, there was a biliribun elevation approaching two-fold the ULN, and this patient had urine toxicology positive for amphetamines, cannabinoids, and morphine.

The LFT abnormalities observed in the Probuphine clinical trial database for patients exposed to Probuphine in addition to sublingual buprenorphine or sublingual buprenorphine alone, were primarily marked transaminase elevations that occurred in patients with baseline LFT abnormalities, underlying viral hepatitis diagnoses, and/or use of concomitant licit or illicit substances that may have had a causal or contributory role. Buprenorphine exposure, alone, or in combination with these other potential etiologies, could be causal as well. In the end, however, the Probuphine safety database reveals no new hepatic safety concerns beyond those previously identified in the clinical trial and postmarketing setting for the marketed sublingual buprenorphine products.

6.1.5.3 QT prolongation

A signal for QT prolongation has been identified in a study of transdermal buprenorphine used for analgesia. The extent of prolongation noted was considered to meet the threshold for regulatory concern, a value which is used to determine whether or not the effect of a drug on the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development. The potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal thorough QT studies.

Electrocardiogram (ECG) data were evaluated for the pooled double-blind and open-label studies.

Table 20 QTcB and QTcF Intervals in Pooled Double-Blind Studies and the All Probuphine Group

Parameter and Visit	Result (msec)	Probuphine N=222 n (%)	Placebo/ SL BPN N=228 n (%)	All Probuphine Group N=262 n (%)
QTcB at Baseline	<450	207 (93.2)	209 (92.9)	244 (93.1)
	450 - <480	9 (4.1)	12 (5.3)	11 (4.2)
	480 - <500	1 (0.5)	3 (1.3)	1 (0.4)
	≥500	2 (0.9)	1 (0.4)	3 (1.1)
QTcB across all visits based on maximal value	<450	191 (86.0)	187 (82.0)	221 (84.4)
	450 - <480	14 (6.3)	25 (11.0)	21 (8.0)
	480 - <500	1 (0.5)	2 (0.9)	2 (0.8)
	≥500	2 (0.9)	2 (0.9)	4 (1.5)
Change from Baseline in QTcB based on maximal value	<30	160 (72.1)	179 (78.5)	177 (67.6)
	30 - <60	28 (12.6)	23 (10.1)	40 (15.3)
	≥60	17 (7.7)	11 (4.8)	23 (8.8)
QTcF at Baseline	<450	209 (94.1)	216 (96.0)	247 (94.3)
	450 - <480	7 (3.2)	8 (3.6)	8 (3.1)
	480 - <500	1 (0.5)	0 (0.0)	1 (0.4)
	≥500	2 (0.9)	1 (0.4)	3 (1.1)
QTcF across all visits based on maximal value	<450	201 (90.5)	204 (89.5)	235 (89.7)
	450 - <480	5 (2.3)	10 (4.4)	9 (3.4)
	480 - <500	0 (0.0)	1 (0.4)	1 (0.4)
	≥500	2 (0.9)	1 (0.4)	3 (1.1)
Change from Baseline in QTcF based on maximal value	<30	170 (76.6)	188 (82.5)	190 (72.5)
	30 - <60	25 (11.3)	16 (7.0)	34 (13.0)
	≥60	10 (4.5)	9 (3.9)	16 (6.1)

Source: Adapted from Integrated Summary of Safety, Table 66, 180–2.

It was noted that based on the maximum value across all the study visits, there were patients with QTcB values ≥ 500, Probuphine n = 2, 0.9%, and Placebo/SL BPN n = 2, 0.9%.

Overall, based on maximum change from baseline, 8% in the Probuphine group and 5% in the placebo/SL group experienced changes of 60 msec or longer. Additionally, some patients had increases exceeding 100 msec.

An evaluation of TEAEs that started on the date of the prolongation or within 3 days afterwards was undertaken, and in general, the type of TEAE reported did not suggest an association with the prolongation in QTc interval. One subject (619-015, 390 msec at baseline to 457 msec) experienced palpitations on the same day of the QT event, also reporting anxiety that day, and another subject experienced somnolence (011-005).

These data confirm that QT prolongation may be seen in patients treated with buprenorphine.

6.1.6 Use of Benzodiazepines

Urine toxicology tests detected use of various substances in addition to opioids. Patients who abuse buprenorphine commonly combine it with benzodiazepines, although this practice is dangerous and has been implicated in buprenorphine-related deaths. Although Probuphine provides pharmacologic treatment only for opioid dependence, the hope and expectation when patients come into treatment for drug addiction is that they will cease using illicit drugs of all kinds. In this study, many patients continued to use benzodiazepines throughout the observation period, as shown in Table 21 below.

Table 21. Benzodiazepine Urine Toxicology Results

	PRO-805				PRO-806				PRO-805/PRO-806 pooled			
	Probuphine (N=108)		Placebo/SL BPN (N = 55)		Probuphine (N=114)		Placebo/SL BPN (N = 173)		Probuphine N=222)		Placebo/SL BPN (N = 228)	
	N	%	N	%	N	%	N	%	N	%	N	%
Weeks 1-4												
Positive	25	(23%)	20	(36%)	39	(34%)	69	(41%)	64	(29%)	89	(40%)
Negative	82	(77%)	35	(64%)	75	(66%)	100	(60%)	157	(71%)	135	(60%)
Missing	1		0		0		4		1		4	
Weeks 5-8												
Positive	22	(22%)	17	(36%)	36	(35%)	55	(39%)	58	(29%)	72	(38%)
Negative	77	(78%)	30	(64%)	67	(65%)	88	(62%)	144	(71%)	118	(62%)
Missing	9		8		11		30		20		38	
Weeks 9-12												
Positive	20	(22%)	10	(30%)	40	(42%)	48	(38%)	60	(32%)	58	(37%)
Negative	72	(78%)	23	(70%)	56	(58%)	77	(62%)	128	(68%)	100	(63%)
Missing	16		22		18		48		34		70	
Weeks 13-16												
Positive	19	(21%)	6	(23%)	31	(33%)	47	(41%)	50	(27%)	53	(38%)
Negative	72	(79%)	20	(77%)	62	(67%)	67	(59%)	134	(73%)	87	(62%)
Missing	17		29		21		59		38		88	
Weeks 17-20												
Positive	26	(31%)	6	(29%)	31	(36%)	43	(40%)	57	(34%)	49	(38%)
Negative	58	(69%)	15	(71%)	55	(64%)	64	(60%)	113	(67%)	79	(62%)
Missing	24		34		28		66		52		100	
Weeks 21-24												
Positive	21	(28%)	7	(35%)	28	(34%)	42	(43%)		(31%)	49	(42%)
Negative	55	(72%)	13	(65%)	55	(66%)	55	(57%)		(69%)	68	(58%)
Missing	32		35		31		76				111	

Table prepared by reviewer from Sponsor's ISS Table 8.5.1

6.2 Safety Summary

In general, the common adverse events associated with Probuphine treatment were similar to those seen with sublingual buprenorphine treatment. The hepatic effects and effects on cardiac conduction were also consistent with buprenorphine's expected effects. The most notable adverse events for Probuphine were related to the implants themselves and to the surgical procedures related to insertion and removal.

In a safety database comprising 262 patients treated with Probuphine, 6 (2%) experienced expulsions or extrusions of implants. Five patients discontinued treatment due to implant-site adverse events. No patients treated with placebo implants experienced expulsions, extrusions, or AEs leading to discontinuation, suggesting that the irritancy of buprenorphine could play a role in these implant site adverse events. More minor implant-site AEs were reported in a significant number of study participants, even after implementation of a modified insertion device and training procedure.

7 Discussion and Points for Consideration

The data on the extent of use of supplemental buprenorphine raise a question of whether Probuphine actually provides the purported advantage over sublingual buprenorphine with respect to diversion and accidental pediatric exposure.

- Patients will likely still require prescriptions for sublingual buprenorphine, which will be present in their homes and represent a risk of abuse, misuse, diversion, and accidental pediatric exposure. In the controlled trials, 40%-62% of Probuphine-treated patients required supplemental buprenorphine, and 11-12% required supplemental buprenorphine even after receiving a fifth implant.
- Over half of patients receiving a fifth implant continued to require supplemental buprenorphine after up-titration. There appear to be patients for whom the studied doses are simply not high enough to manage their subjective symptoms.
- Almost all patients continued to have periodic positive urine tests for illicit opioids. If urine test results, rather than subjective symptoms, had been the criterion for offering additional buprenorphine, potentially more patients may have required it. Moreover, the protocols permitted very limited take-home medication; patients might have been more inclined to request supplemental medication had take-home supplies been permitted. It is likely that, in clinical practice, physicians will prescribe sublingual buprenorphine for use "as-needed." In this situation, monitoring procedures such as pill counts would be ineffective for detecting inappropriate use or diversion, and household contacts would continue to be at risk for exposure to buprenorphine.

It is not clear whether the risks of the Probuphine insertion and removal procedures have been adequately characterized, and whether the safety experience in clinical trials can be extrapolated to the post-marketing setting.

- Experience with inserting and removing Probuphine implants is limited to the 262 patients who participated in the clinical studies. The 228 patients who received placebo implants provide some additional experience with the procedures. Of these implantation/removal experiences, about half were performed under conditions using a different physician training procedure and different insertion device than the one currently proposed. This is not a large safety database, and even in this limited population, there were examples of patients who had to return for a second visit in order to fully remove rods, patients who experienced rods protruding through the skin, and patients experiencing infections or other complications at the implant site. Frequently, the rods were broken at the time of removal, potentially complicating the removal process. It's worth noting that the target population for this product is significant: 1 million patients received a dispensed prescription for sublingual buprenorphine during 2012.
- Each site in the clinical trial typically identified a limited number of "implanting physicians" who received training and performed all of the implantation procedures. Over half of the insertions and two-thirds of the removals in study PRO-806 (performed under the "improved" training procedures and using the new insertion device) were performed by physicians from surgically-related medical specialties. The share of sublingual buprenorphine prescriptions written by physicians from surgical specialties in 2012, by contrast, was less than 10%. This

mismatch between the skills, training, and experience of the clinicians who performed the procedures in the clinical trials and the clinicians currently engaged in buprenorphine treatment suggests that one of two things is likely to occur: (1) Probuphine implantation procedures will be undertaken by physicians without appropriate skills, training, and experience in performing surgical procedures; or (2) Probuphine implantation procedures will be undertaken by physicians without appropriate skills, training, and experience in treating patients for opioid addiction using buprenorphine. The most likely scenario seems to be a "divided" model of care in which the implanting physician takes no responsibility for ongoing management, and the physician managing the addiction treatment is not familiar with how to address implantation site complications.

Unanswered questions remain concerning how long Probuphine treatment can be continued.

- The clinical trials involved implantation for 24 weeks, with some patients continuing into open-label extensions for an additional 24 weeks. Agonist treatment of opioid dependence, for many patients, is a potentially life-long prospect. There are certain unanswered questions about the potentially indefinite use of Probuphine.
    - The patients who continued into the open-label extensions were treated with sublingual buprenorphine for a period of time and then the implant was placed in the opposite arm. However, the proposed labeling advises that implantation into a new site can occur immediately after the previous implant is removed. There are no data to support this advice.
    - All of the training materials used in the clinical development program and those that have been developed for use during marketing train the implanting clinician to locate a single implantation site on each arm. The Applicant asserts there may be room for two implantation sites in each arm; however, there are no data supporting the practice of locating and using a site that is superior or inferior to the site that clinicians have been heretofore trained to use.
    - Moreover, after all sites have been used—whether there are two sites or four—there is no information about whether Probuphine can be re-placed into a previously-used, likely scarred site. The bioavailability of Probuphine could be altered by scarring at previously-used sites. This has not been evaluated.

There is little information about patient experience at the end of Probuphine treatment.

- Post-treatment visits did not continue for long after treatment ended, and patients do not seem to have been routinely monitored for the emergence of withdrawal symptoms. There is little information about what happens after treatment ends, either because the implant is removed or because a patient doesn't return for removal, but the implant eventually ceases eluting drug. Because the buprenorphine withdrawal syndrome is sometimes delayed in its emergence, the duration of post-treatment

monitoring may have been insufficient to characterize the nature of withdrawal experienced by patients at the end of treatment.

There is little information about the risks to the patient should the implants never be removed.

- Patients who were lost to follow-up did not have implants removed. The number of patients who end up not having the implants removed could be a more significant issue in the post-marketing setting if patients are required to pay for the removal procedure.

It is not clear that the Risk Mitigation and Evaluation Strategy proposed by the Applicant is realistic and sufficient to manage risks.

- The Division of Risk Management has identified a number of concerns about the proposed REMS, which are documented in their memo dated February 21, 2013.

Ultimately, it is necessary to weigh the benefits against the risks, either known or not-yet-characterized. Does Probuphine work well enough to outweigh these concerns?

- Probuphine-treated patients were more likely than patients treated with placebo to complete the study and were less likely to require the frequency of sublingual buprenorphine administration that met criteria for "treatment failure."
    - However, only 32% of Probuphine-treated patients in Study PRO-805 and 27% in Study PRO-806 submitted opioid-negative samples for even half of the urine tests.
    - On the other hand, 23% of the Probuphine-treated treated patients in Study PRO-805 and 27% in Study PRO-806 had 5% opioid-negative samples or fewer.
    - Even after for allowing for four months of "grace period," only 29% of Probuphine-treated patients in Study PRO-805 and 23% in Study PRO-806 submitted opioid-negative samples for even half of the urine tests during the last two months of treatment. Applying a stricter definition of 75% opioid-negative samples after four months of "grace," 14% in PRO-805 and 16% in PRO-806 would be considered responders.
- The dose of buprenorphine delivered by 4 Probuphine implants is less than a third of the dose delivered by 16 mg sublingual buprenorphine. It is possible that the dose is sufficient to provide some agonist effects but not to block the effects of exogenous opioids. Potentially, Probuphine could deliver just enough buprenorphine to allow patients to continue to use illicit opioids without experiencing withdrawal when they stop. Patients who do not considerably modify their drug-taking behavior may not accrue significant benefit from Probuphine treatment.

8 Appendix A: Drug Addiction Treatment Act of 2000

The Narcotic Addict Treatment Act of 1974 limits methadone maintenance treatment to the context of the Opioid Treatment Program (OTP) (i.e., methadone clinic) setting. Methadone treatment of opioid addiction is delivered in a closed distribution system that originally required special licensing by both Federal and State authorities. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases.

Because this is the setting where addiction treatment was delivered for decades, most U.S. physicians have little experience and expertise in the treatment of opioid addiction.

The Title XXXV of the Children's Health Act of 2000 (P.L. 106-310) provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8 hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine.

9 Appendix B: Supplemental Sublingual Buprenorphine Use

Table 22. Summary of Supplemental Buprenorphine Use (Intent-to-Treat Population)

Study	Treatment Group	Number(%) Subjects Requiring Supplemental SL Buprenorphine	Number(%) Subjects Requiring Fifth Implant
PR0-805	Probuphine	67 (62.0)	22 (20.4)
	Placebo	50 (90.9)	32 (58.2)
PR0-806	Probuphine	45 (39.5)	25 (21.9)
	Placebo	36 (66.7)	21 (38.9)
	SL buprenorphine	7 (5.9)	Not allowed
PR0-807	Probuphine	26 (41.9)[a]	6 (9.7)[a]
PR0-811	Probuphine	17 (20.0)[a]	9 (11.0)[a]
TTP-400-02-01	Probuphine- 2 implants	3 (50.0)	Not allowed
	Probuphine- 4 implants	2 (33.3)	Not allowed
PR0-810	SL buprenorphine; Probuphine	0 (0)	Not allowed

SL = sublingual.
[a] Percentage relative to full study (safety) population, which includes subjects previously treated with SL buprenorphine in Study PRO-806, for a total denominator of n=85 subjects.
Source: Integrated Summary of Efficacy, p. 57

Table 23. Summary of Mean Supplemental SL Buprenorphine Use, Studies PRO-805 & PRO-806 (Intent-to-Treat Population)

	Subjects Receiving 4 Implants		**Subjects Receiving 5 Implants, Before Implant**		**Subjects Receiving 5 Implants, After Implant**	
	Probuphine	**Placebo**	**Probuphine**	**Placebo**	**Probuphine**	**Placebo**
Double-Blind Studies						
Total number of subjects	**175**	**56**	**47**	**53**	**47**	**53**
Number (%) of subjects requiring supplemental SL buprenorphine	65 (37.1)	33 (58.9)	47 (100.0)	53 (100.0)	26 (55.3)	42 (79.2)
Days Used/Week	0.23	0.88	2.03	3.54	0.46	2.16
mg Used/Week	2.61	10.40	23.11	37.72	6.06	25.04

Source: Integrated Summary of Efficacy, p. 58

10 Appendix C: Common Adverse Events in Buprenorphine Studies Listed in Approved Labeling

ADVERSE REACTIONS

In a comparative study, adverse event profiles were similar for subjects treated with 16 mg buprenorphine and naloxone sublingual tablets or 16 mg buprenorphine HCl sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4-week study.

Adverse Events (≥ 5%) by Body System and Treatment Group in a 4-week Study

	N (%)	N (%)	N (%)
Body System /Adverse Event (COSTART Terminology)	**Buprenorphine and Naloxone Sublingual Tablets 16 mg/day N=107**	**Buprenorphine HCl Sublingual Tablets 16 mg/day N=103**	**Placebo N=107**
Body As A Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)

Adverse Events (≥ 5%) by Body System and Treatment Group in a 4-week Study

	N (%)	N (%)	N (%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15%)
Nausea	16 (15%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14%)	13 (12.6%)	11 (10.3%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. The table below shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

Adverse Events (≥ 5%) by Body System and Treatment Group in a 16-week Study

Body System /Adverse Event (COSTART Terminology)	Buprenorphine Dose*				
	Very Low* (N=184)	Low* (N=180)	Moderate* (N=186)	High* (N=181)	Total*(N=731)
	N (%)	N (%)	N (%)	N (%)	N (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)

Adverse Events (≥ 5%) by Body System and Treatment Group in a 16-week Study

Body System /Adverse Event (COSTART Terminology)	Buprenorphine Dose*				
	Very Low* (N=184)	Low* (N=180)	Moderate* (N=186)	High* (N=181)	Total* (N=731)
	N (%)	N (%)	N (%)	N (%)	N (%)
Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes: “Very low” dose (1 mg solution) would be less than a tablet dose of 2 mg; “Low” dose (4 mg solution) approximates a 6 mg tablet dose; “Moderate” dose (8 mg solution) approximates a 12 mg tablet dose; “High” dose (16 mg solution) approximates a 24 mg tablet dose.

Contraceptive Implants – Regulatory History and Lessons Learned

Background

All implantable methods of contraception offer long-acting reversible contraception and are > 99% effective in preventing pregnancy. Four iterations of contraceptive implants have been approved for marketing in the United States, with each new generation featuring product designs aimed at improving tolerability. These implants contain a progestin (either levonorgestrel or etonogestrel), which is released over time.

Regulatory and Marketing History of Implantable Contraceptives

Norplant, the six-capsule levonorgestrel contraceptive implant system, was the first contraceptive implant to be approved in the U.S. in 1990; it was approved for up to 5 years of continuous use. Norplant consists of six, sealed silicone capsules which are placed in a fan shaped pattern in the medial aspect of the upper arm. Each capsule is 2.4 mm in diameter and 34 mm long.

In Norplant's first full year on the U.S. market, insertions were running at about 800 per day; by the beginning of 1993, one million U.S. women had become Norplant users.[1] In March 1994, negative media coverage on Norplant removal difficulties began to affect usage.[2] By 1996, annual U.S. Norplant insertions had decreased by 90 percent.[1] U.S. marketing of Norplant was discontinued in 2002. In contrast, Norplant continues to be marketed in developing countries.[3,4]

Norplant II (Jadelle), is a two-capsule levonorgestrel implant approved by the FDA for 3 years continuous use in 1996. The dosing duration was expanded to 5 years of continuous use in 2002. Despite the FDA approval, Norplant II has never been marketed in the U.S.

In 2006, the first single-capsule contraceptive implant (Implanon) was approved. Implanon was replaced by Nexplanon (Implanon NXT) in 2011. In Nexplanon, the capsule is made of ethylene vinylacetate copolymer; each is 2 mm in diameter and 40 mm long. Nexplanon is approved for up to 3 years of continuous use. It has 15mg of barium sulphate added to the core, so it is detectable by X-ray. Nexplanon also has a pre-

[1] Kolata G. (1995, may 28). Will the lawyers kill off Norplant? *The New York Times.*
[2] National Research Council. (1998) *Free Executive Summary*, Appendix B, *Contraceptive Research, Introduction, and Use: Lessons from Norplant.* Washington, D.C. The National Academies Press. Harrison PF, Rosenfield A, editors.
[3] (1998, September 5) Contraceptive Maker Wins Woman's Suit Over Side Effects. *The New York Times.*
[4] Morrow, DJ. (1999,August 27). Maker of Norplant Offers a Settlement in Suit Over Effects. *The New York Times*.

loaded applicator for easier insertion. Currently, Nexplanon is the only contraceptive implant marketed in the U.S.

The subdermal implant system utilized for delivering buprenorphine (Probuphine) is similar to the Norplant system.

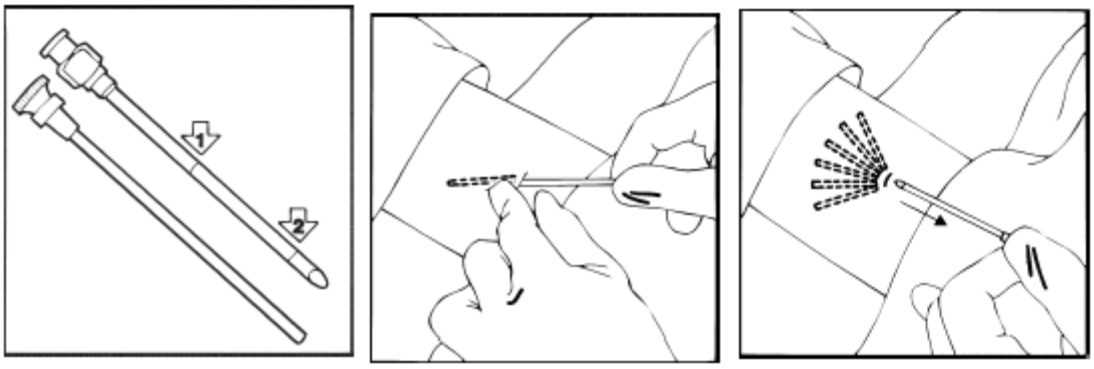
Description of Insertion and Removal Procedures

Norplant

Insertion:

The patient lies on her back on the exam table with her non-dominant arm flexed at the elbow and externally rotated so that her hand is at the level of her head. After cleaning the area with antiseptic solution and applying local anesthesia, the six capsules are inserted subdermally through a 2-mm incision and positioned in a fanlike manner with the fan opening towards the shoulder. The optimal insertion area is on the medial side of the upper arm, about 8 to 10 cm above the elbow crease.

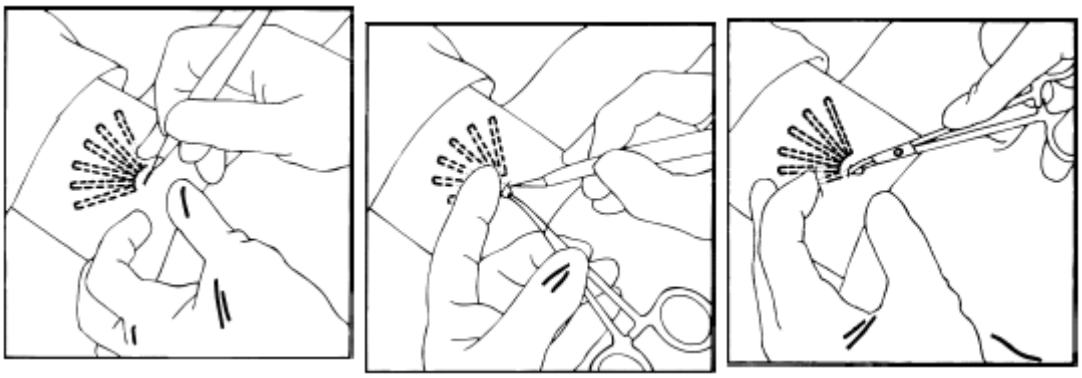
The six capsules are placed subdermally, one at a time, via a trocar. The trocar has two markings on it: the first mark is closer to the hub and indicated how far the trocar should be introduced under the skin before the loading of each capsule; the second mark is close to the tip and indicates how much of the trocar should remain under the skin following the insertion of each implant. The bevel of the trocar is oriented up toward the skin to keep the capsule in a superficial plane.



The trocar is not removed from the incision until all capsules have been inserted. The correct position of the capsules can be ensured by palpation after the insertion has been

completed. After placement of the sixth capsule, sterile gauze may be used to apply pressure to the insertion site to ensure hemostasis.

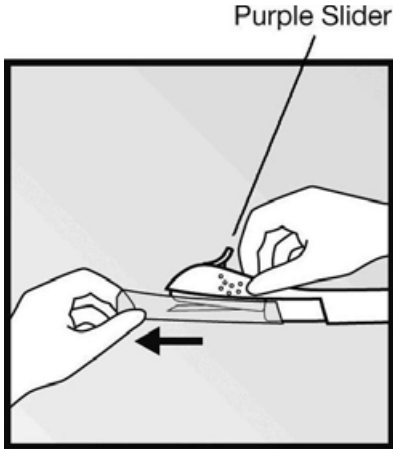
Removal:
Once all six capsules are located by palpation, a small amount of local anesthetic is applied to the original incision site. A 4-mm incision is made with the scalpel close to the ends of the capsules. Each capsule is pushed gently towards the incision. When the tip of a capsule is visible near the incision, it is grasped with mosquito forceps and retrieved.



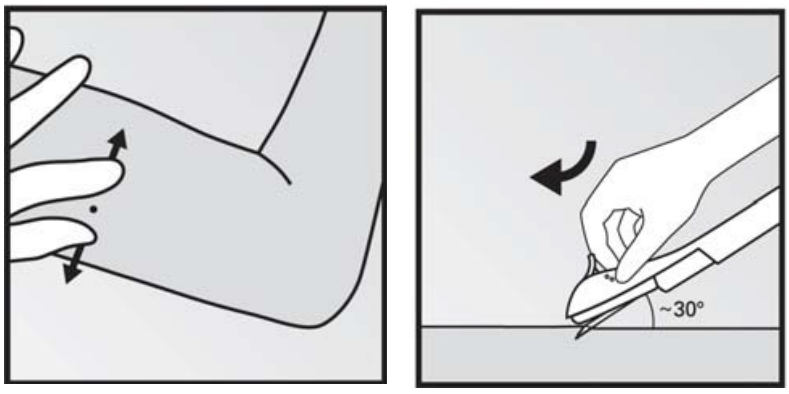
Should minor dissection be necessary to free up the capsules, a scalpel or forceps can be used to gently open the tissue sheath that has formed around the capsule. The capsule is removed from the incision with the second pair of forceps. Steri-strips are applied to the incision once the procedure is completed.

Nexplanon
The insertion and removal procedures for Nexplanon are included for comparison with Norplant.

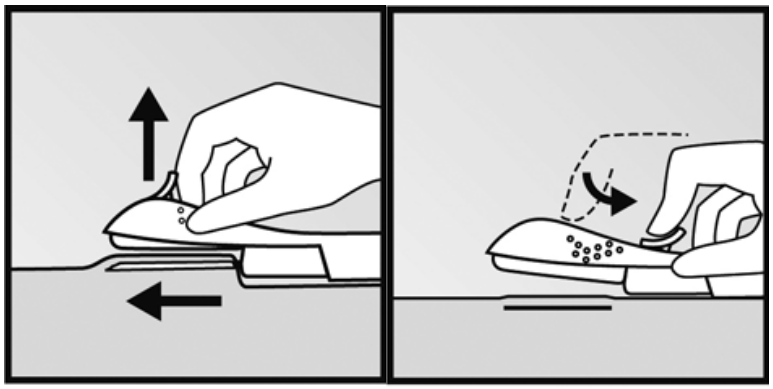
Insertion:
Insertion of Nexplanon is in the same area of the non-dominant arm as Norplant. This area is prepped with antiseptic solution and local anesthesia is applied. A sterile, disposable Nexplanon applicator, preloaded with the implant, is removed from its blister pack. The applicator is held above the needle and the transparent protection cap is removed by sliding it horizontally in the direction of the arrow away from the needle.



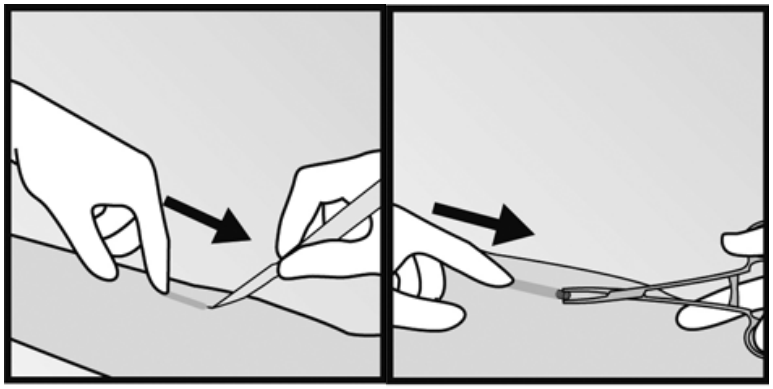
After stretching the skin with the free hand, the skin is punctured with the tip of the needle at a 30° angle.



The applicator is then lowered to a horizontal position. With the skin tented by the tip of the needle, the needle is inserted to its full length. The purple slider is then unlocked and moved fully backward. The implant is now in its final subdermal position, and the needle is locked inside the body of the applicator. The applicator can now be removed.



Removal:
After applying antiseptic solution and local anesthesia, the implant is located by palpation. The proximal end of the implant is pushed down to stabilize it. Starting at the distal tip of the implant, a longitudinal, 2-mm incision is made towards the elbow. The implant is grasped with curved mosquito forceps and gently removed. Steri-strips are applied to the incision.



Insertion and Removal/Device Related Adverse Events

The Norplant label describes the nature and frequency of adverse events related to insertion and/or removals as follows:

- Removal difficulties affecting subjects (based on 849 removals): 6.2%
- Pain or itching near implant site (usually transient): 3.7%
- Infection at the implant site: 0.7%

With respect to literature, one comprehensive review[5] on adverse events from clinical trials for Norplant and other implantable progestins is summarized below:

- Removal complications occurred in up to 14.8% of users, mostly due to fibrous pericapsular sheath formation around the implant or due to implant breakage, deep placement or migration. In 0.8% of users, the procedure required a second incision or was not successful, i.e. not all the implanted rods could be removed.
- Removal complications in comparative studies between Norplant and Jadelle (two rods) were 6.9% for Jadelle and 14.8% for Norplant, respectively.
- Removal complications in comparative studies between Norplant and Implanon (single rod), were 0.2% for Implanon and 4.8% for Norplant, respectively.
- Infection rates with Norplant insertion in most studies were less than 0.5%, but two studies reported infection rates 1% or greater. Most infections occurred within the first two months (65%), but infections have been reported two years after insertion.

[5] Brache V, Faundes A, Alvarez F, Cochon L. Nonmenstrual adverse events during use of implantable contraceptives for women: data from clinical trials. Contraception 2002 Jan;65(1):63-74.

- For all implants, the rate of spontaneous expulsion was 0-0.6% in the absence of infection. When spontaneous expulsions occur, 35.7% occur within the first two months and 70% occur within first four months after insertion.
- Nerve damage was reported in 0.7-7.1% of users, including pain or numbness at the implant site or arm for any implant.
- In one study, US Norplant users were interviewed and 28% reported pain in the implant arm; pain was cited as the reason for implant removal in up to 2% of users.
- Other insertion complications were reported in 0-1.7% of users, such as bleeding, hematoma, allergy to anesthetic or bandages, or dizziness.

Examples of reports that describe significant, Norplant device-related adverse events in the literature include several cases of ulnar neuropathy involving the musculocutaneous and antebrachial cutaneous nerves.[6,7,8]

Compared to Norplant, the newer iterations of implants appear to be better tolerated. A meta-analysis of data from seven open-label, randomized studies in 1,378 women compared the ease of insertion and removal of the Implanon and Norplant implants and the frequency of associated complications.[9] When done by trained providers, it was approximately four times quicker to insert and remove Implanon than Norplant (mean insertion times 1.1 vs. 4.3 min, respectively; mean removal times 2.6 vs. 10.2 min, respectively). Insertion complications were very rare with both Implanon (0.3%) and Norplant (0.0%). However, Implanon was associated with a significantly lower frequency of removal complications (0.2 vs. 4.8% with Norplant; $p< 0.001$).

Finally, adverse event data for Norplant in the FDA Adverse Event Reporting System (FAERS)[10] were reviewed. This database was searched for all Norplant U.S. reports with the serious outcome disability received from 10 December 1990 (U.S. approval) until 06 February 2013. Forty-three cases of women reporting a disability related to the Norplant device were identified. The disabling event(s) reportedly occurred following device removal in 25 cases, insertion in 13 cases, and both insertion and removal in 2 cases. The

[6] Smith JM, Conwit RA, Blumenthal PD, Ulnar nerve injury associated with removal of Norplant implants. Contraception 1998 Feb;57(2):99-101.
[7] Hueston WJ, Locke KT. Norplant neuropathy: peripheral neurologic symptoms associated with subdermal contraceptive implants. J Fam Pract 1995 Feb;40(2): 184-6.
[8] Marin R, McMillian D, Ulnar neuropathy associated with subdermal contraceptive implant, South Med J 1998 Sep;91(9):875-8.
[9] Power J, French R, Cowan FM, Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy. Cochrane Database Syst Rev 2007 Jul 18;(3):CD001326.
[10] FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

remaining three cases had limited information. The cases generally reported paresthesia, dysesthesia or pain. Some users also reported decreased grip strength, restricted range of motion, or being unable to fully extend their arm. These reported events substantially limited one or more major life activities, such as caring for oneself, performing manual tasks, eating, and working. Where reported, the diagnoses included: ulnar nerve injury (11 cases), medial cutaneous nerve injury (5), "nerve damage" (3), injury to both the ulnar and medial cutaneous nerve (2).

In summary, contraceptive implants occasionally cannot be removed by palpation. In other cases implants were not implanted or were extruded because of faulty trocar placement. Other reports indicate that implants migrated to other parts of the body, including the chest and other locations in the arm. Implants also have been inserted into the vascular system and a case of migration to the pulmonary artery with Implanon was reported in FDA's FAERS database.

When the implants cannot be located by either visual inspection or palpation, additional imaging technologies such as ultrasound, high-resolution fluoroscopy with digital subtraction imaging, MRI, and compression film screen mammography have been used to locate the implants for removal.[11,12,13,14] In the cases where imaging technology is necessary, dissection is often necessary to remove the implant. In other cases, general anesthesia was necessary to allow extensive dissection in the arm to remove an implant imbedded in fibrous tissue.[15] Finally, Nexplanon can be located by X-ray. Neither Norplant nor Probuphine can be located by X-ray methodology.

[11]Letterie GS, Garnaas M, Localization of "lost" Norplant capsules using compression film screen mammography, Obstet Gynecol 1995 May;85(5 Pt 2):886-7.
[12] Silverstein MI, Lewis CA, Sheline ME, Sarma SP. Fluoroscopically guided Norplant removal, J Vasc Interv Radiol 2001 Feb; 12(2):253-5.
[13] Crist T, Barnes MR, Whitehurst WC. Difficulty finding and removing a Norplant capsule. NC Med J 1994 Feb;55(2):76.
[14] Thurmond AS, Weinstein AS, Jones MK, Jensen JT, Nichols MD. Localization of contraceptive implant capsules for removal. Radiology 1994 Nov;193(2):580-1.
[15] Wechselberger, G, Wolfram D, Pülzl P, Soelder E, Schoeller T. Nerve injury caused by removal of an implantable hormonal contraceptive. Am J Obstet Gyneol 2006 Jul;195(1):323-6. Epub 2006 Apr 21.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: **February 21, 2013**

To: **Members of the Psychopharmacologic Drugs Advisory Committee (PDAC)**

From: **Division of Risk Management**
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology (OSE)

Subject: **Summary of Sponsor's Proposed Risk Evaluation and Mitigation Strategy (REMS) for Probuphine**

Product: **Probuphine (buprenophine HCl/ethylene vinyl acetate) subdermal implant (NDA 204-442)**

1 INTRODUCTION

This memorandum from the Division of Risk Management (DRISK) summarizes and provides preliminary feedback on the proposed risk evaluation and mitigation strategy (REMS) proposed by Titan Pharmaceuticals (Titan) for Probuphine (buprenorphine HCl/ethylene vinyl acetate) subdermal implant, NDA 204-442. This memorandum is based on the proposed REMS submitted by Titan with the NDA application, received October 31, 2012, and does not include information presented to the Advisory Committee that has not been submitted for Agency review as of February 19, 2013.

2 BACKGROUND

2.1 Risk Evaluation and Mitigation Strategies (REMS)[1]

The Food and Drug Administration Amendments Act (FDAAA) provides FDA authority to require risk evaluation and mitigation strategies (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks [FDAAA Section 505-1(a)]. A REMS is a required risk management plan that uses risk minimization strategies beyond professional labeling.

[1] .FDA Draft Guidance for Industry – *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, dated September 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf

REMS may include one or more of the following: A Medication Guide (MG) or patient package insert for patients, a communication plan (CP) for health care providers (HCPs), and Elements to Assure Safe Use (ETASU), which often involve some form of restricted distribution and or evidence of safe-use conditions.

A Communication Plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. For example, "Dear Healthcare Professional" letters, collaboration with professional societies, brochures focusing on the important risk messages, and other educational materials have been required to alert prescribers to serious risks associated with the use of certain drugs and biologics.

ETASU can include one or more of the following requirements:

- HCPs who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;
- The drug be dispensed to patients only in certain health care settings;
- The drug be dispensed to patients with evidence or other documentation of safe-use conditions;
- Each patient using the drug be subject to certain monitoring; or
- Each patient using the drug be enrolled in a registry.

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling [FDAAA Section 505-1 f(1)(A)].

The statute [FDAAA Section 505-1(d)] also requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

2.2 Drug Addiction Treatment Act of 2000 (DATA 2000)[2]

The Drug Addiction Treatment Act of 2000 (DATA 2000) allows qualified physicians to obtain a waiver from the registration requirements of the Controlled Substances Act (CSA) to prescribe and dispense opioid medications in Schedule III, IV, and V for the treatment of opioid addiction provided such medications are approved by FDA for that indication. To qualify for a waiver under DATA 2000, physicians must hold a current state medical license, a valid registration number with the Drug Enforcement Agency (DEA), and meet one or more of the following conditions:

- The physician holds a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.

[2] Substance Abuse and Mental Health Services Adminsitration. Buprenorphine – Drug Addcitin Treatment Act of 2000. Available at: http://buprenorphine.samhsa.gov/titlexxxv.html Accessed February 20, 2013.

- The physician holds an addiction certification from the American Society of Addiction Medicine.
- The physician holds a subspecialty board certification in addiction medicine from the American Osteopathic Association.
- The physician has completed not less than eight hours of training with respect to the treatment and management of opioid-addicted patients. This training can be provided through classroom situations, seminars at professional society meetings, electronic communications, or otherwise. The training must be sponsored by one of five organizations authorized in the DATA 2000 legislation to sponsor such training, or by any other organization that the Secretary of the Department of Health and Human Services (the Secretary) determines to be appropriate.
- The physician has participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in Schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary by the sponsor of such approved drug.
- The physician has other training or experience, considered by the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) to demonstrate the ability of the physician to treat and manage opioid-addicted patients.
- The physician has other training or experience the Secretary considers demonstrates the ability of the physician to treat and manage opioid-addicted patients.

To obtain a waiver a qualified physician must notify the Center for Substance Abuse Treatment (CSAT), a component of the Substance Abuse and Mental Health Services Administration (SAMHSA), of their intent to begin dispensing or prescribing this treatment and contain their qualifications required to do so. The physician must also attest that they will refer addiction treatment patients for appropriate counseling and other non-pharmacologic therapies and will have no more than 30 addiction treatment patients under their care at any one time unless, at least one year from the date the physician provided initial notification, a second notification is submitted to the Secretary stating the need and intent to treat up to 100 patients.

2.3 FDA Approved Buprenorphine Products for the Treatment of Opioid Dependence

Currently, Subutex® (buprenorphine HCl) sublingual tablets and Suboxone® (buprenorphine HCl/ naloxone HCl) sublingual tablets and sublingual film are approved for the treatment of opioid addiction. These products were the first narcotic drugs available for the treatment of opioid dependence in an office-based treatment program under DATA-2000. Subutex is intended for the induction phase of treatment for opioid addiction. Suboxone is intended for use in maintenance treatment of opioid addiction. Naloxone has been added to Suboxone to guard against intravenous abuse of buprenorphine by individuals physically dependent on opioids.

Subutex and Suboxone are approved with a REMS to ensure the benefits of the drug outweigh the risks. In particular, the Agency determined that these products could only be approved if ETASU are required as part of a REMS to mitigate the risks of (1) exposure to Subutex/ Suboxone in persons for whom it was not prescribed, including accidental exposure in children, and (2) risks of abuse and misuse, listed in the labeling. The elements to assure safe use will inform patients of the serious risks associated with Subutex/Subuxone and the appropriate

conditions of safe use and storage of Subutex/Suboxone. The ETASU will also ensure adequate clinical monitoring of patients by healthcare providers.

The goals of the REMS for Subutex and Suboxone are to:

- Mitigate the risks of accidental overdose, misuse and abuse
- Inform patients of the serious risks associated with Subutex/Suboxone

The elements of the REMS include a Medication Guide, ETASU that include documentation of safe use conditions and ongoing monitoring requirements, and an implementation system. The REMS does not link prescribing or dispensing to documentation of safe use conditions and monitoring elements (e.g., is not a restricted distribution program).

2.4 Probuphine (Buprenophine HCl/ethylene vinyl acetate) subdermal implant : General Product Information

Probuphine is a Schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The Sponsor is seeking approval of Probuphine for the maintenance treatment of opioid dependence and should be used as part of a complete treatment program, including counseling and psychosocial support. Probuphine is available as a 25 mm x 2.5 mm rod-shaped implant and contains 80 mg buprenorphine HCl. Once implanted subdermally at the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus), it provides sustained delivery of buprenorphine for up to six months.

Probuphine was developed as an alternative for practitioners and patients in the office based setting utilizing an abuse deterrent formulation. Probuphine is intended for use in patients who are opioid-tolerant and who are stabilized on a sublingual buprenorphine daily dose of 12-16 mg for a period of at least 3 consecutive days. After induction with sublingual buprenorphine, four Probuphine implants are surgically inserted subdermally in the upper arm. After 2 weeks of therapy, the patient is assessed to determine if a fifth implant is necessary to achieve appropriate therapeutic drug levels. Probuphine is removed after six months; new implants can be inserted in the opposite arm if continued therapy with Probuphine is warranted.

3 SERIOUS SAFETY CONCERNS FOR PROBUPHINE

Due to the novel formulation of Probuphine, it is associated with serious complications related to improper technique associated with the implantation procedure, including removal. Complications related to the implantation procedure may include, but are not limited to, surgical complications, infection, and overdosing/underdosing. Additionally, while the novel formulation reduces the risk for potential abuse, misuse, and accidental exposure, these risks are not eliminated. Due to the nature of the intended patient population (i.e., patients who abuse opioids), a potential concern is that patients may intentionally remove the implants after insertion to obtain access to buprenorphine for purposes of abuse and misuse. Additionally, patients may be accidentally exposed to buprenophine from spontaneous expulsion of the implant, which can occur any time after insertion.[3]

If Probuphine is approved, a risk mitigation strategy (beyond professional labeling) is likely to be required to address (1) the risk of complications resulting from improper technique associated

[3] Refer to the FDA "Efficacy and Safety Background" in the Background Package for a complete description of the safety profile from the clinical trials submitted to the Probuphine NDA.

with the implantation procedure of Probuphine, including removal, and (2) the risk of abuse, misuse, and accidental exposure.

4 SPONSOR'S PROPOSED REMS FOR PROBUPHINE

Titan has submitted a proposed REMS for Probuphine with the NDA application, received October 31, 2012. The goals of the proposed REMS are:

1. To maximize effective Probuphine therapy by optimizing the following:
    - patient selection,
    - patient monitoring,
    - insertion and removal procedures by educating healthcare professionals, (Drug Abuse Treatment Act [DATA 2000]-waived physicians and other healthcare providers trained by Titan to perform the Probuphine insertion and removal procedures),
    - implementing a closed process to adequately control distribution and dispensation.
2. To ensure safe use of Probuphine by minimizing the risk of misuse, abuse, diversion, accidental poisonings, overdose and complications related to Probuphine and the insertion and removal procedures.

The components of the sponsor's proposed REMS include a MG, CP, ETASU, and an Implementation System.

The Medication Guide will be included with each package of Probuphine. The prescribing physician will be expected to provide the Medication Guide and counsel the patient on the important safety information for Probuphine prior to the implantation procedure. Additionally, Titan has proposed to implement a CP which will include a letter to currently registered prescribers of buprenorphine and letter to organizations that provide certification and training for healthcare professionals in the office based treatment of opioid dependence with buprenorphine. These letters will provide an orientation to Probuphine and the REMS training requirements.

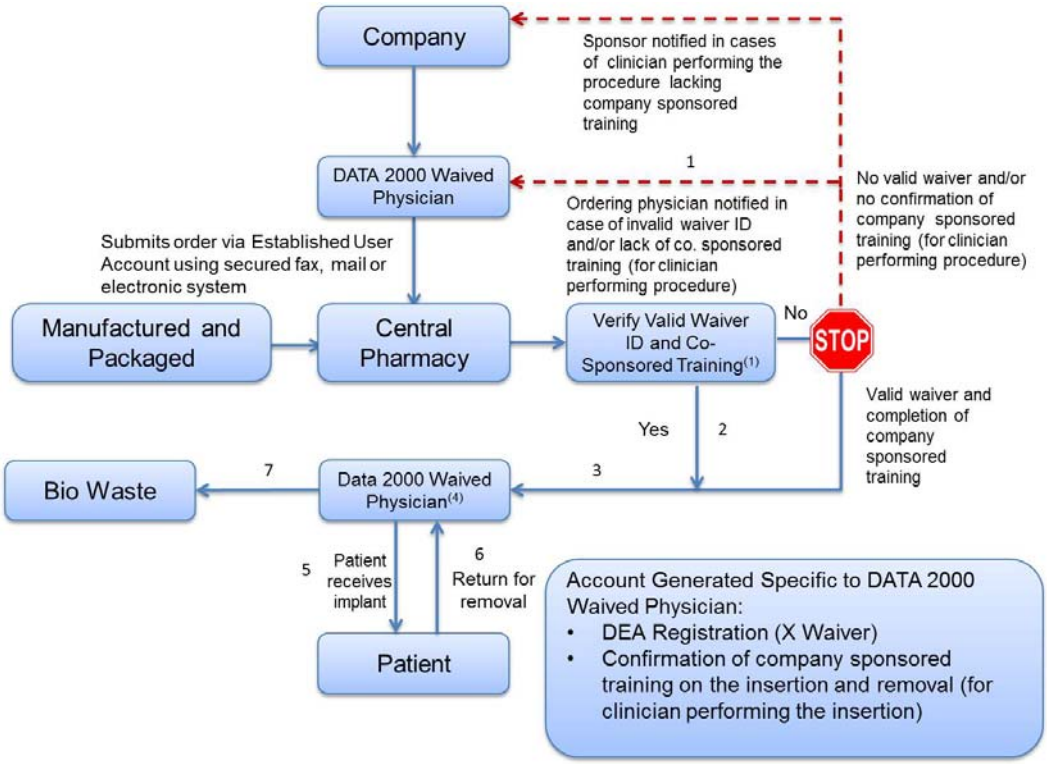
The Sponsor has proposed the following ETASU to mitigate the risks associated with Probuphine:

- HCP certification: HCPs who insert and remove Probuphine will be formally trained via a company sponsored program on the appropriate implantation/removal techniques, proper patient selection, and safe use of Probuphine.
- Pharmacy certification: A central pharmacy will be utilized to dispense Probuphine directly to DATA-2000 waived physicians within a closed distribution system. The pharmacy will be responsible for verifying that the prescribing physician is DATA-2000 waived and that the HCP who will perform the implantation/removal procedure is REMS certified.
- Documentation of safe use conditions: DATA-2000 waived physicians will record the ordering and receipt of Probuphine from the pharmacy via a distribution log. REMS certified HCPs will be required to document implantation and removal of Probuphine for individual patients. Additionally, patients will be provided a Patient

Identification Card to document the date of implantation, number of implants, location of implants, etc.

Titan's proposed process within the health care system, or "model of care", for Probuphine is presented in Figure 1 below:

Figure 1: Proposed Distribution and Dispensing System for Probuphine



1: Prescribing physician must have a DATA-2000 waiver ID number and the HCP performing the procedure must be REMS certified. Note: The prescribing physician and HCP performing the procedure may not be the same individual.

2: Date of order request and number of Probuphine ordered is documented on a distribution log.

3: Data-2000 waived physician or authorized designee accepts delivery of Probuphine from the pharmacy. Date and number of Probuphine received are recorded on the distribution log and Probuphine is stored in a securely.

4: The DATA-2000 waived physician must notify the local DEA office if theft or loss of Probuphine occurs.

5: Probuphine is inserted in the patient by a REMS certified HCP. If the HCP performing the implantation procedure is not DATA-2000 waived, the procedure must be performed in the presence of the DATA-2000 waived prescriber. The date and time of the implantation procedure is documented

6: Probuphine is removed by a REMS certified HCP. If the HCP performing the removal procedure is not DATA-2000 waived, the procedure must be performed in the presence of the DATA-2000 waived prescriber. The date and time of the removal procedure is recorded documented. For patients who never return for removal, the DATA 2000 waived physician and/or office staff will make three attempts to contact the patient and request return to the office for removal; these attempts must be documented

7: Used Probuphine should be disposed of according to appropriate procedures with other medical wastes. The date and time of disposal of Probuphine is documented.

5 SUMMARY OF AGENCY'S PRELIMINARY COMMENTS ON THE PROPOSED REMS FOR PROBUPHINE

The proposed model of care by Titan is designed to provide adequate training to clinicians regarding the implantation and removal procedure of Probuphine, including associated complications. However, the Agency has identified several inadequacies for the proposed REMS.

1. The Sponsor has not provided any data (e.g., stakeholder input, input from DEA, input from SAMHSA) to validate the proposed model of care. Additionally, while the proposed model of care may represent the predominant health care setting, it does not consider various other potential models of care. Below are some examples of other settings or potential models of care:
    a. Probuphine is expected to be utilized in opioid treatment programs by qualified prescribers. However, the proposed model does not take into account the paradigm of patient management for this setting (e.g., drug distribution, training requirements).
    b. The proposed model assumes the prescribing physician will have the expertise at his/her healthcare facility to insert and remove the implant. However, based on the spectrum of specialties currently treating patients with opioid addiction under DATA-2000, the Agency anticipates that prescribers that do not have expertise at their respective facility will prefer to leverage expertise from other resources within the healthcare system.
2. The Sponsor has not provided any data (e.g., stakeholder input, human factors testing) to validate the training program. The training program was instituted in Study PRO-806, PRO-810, and PRO-811 due to the number of improper implantation/ removal procedures reported in clinical trials. While the clinical trials did demonstrate an improvement in complications after the institution of the training program, the Sponsor's submission indicates that the training materials are still in development and in a pilot phase. Therefore, sufficient data has not been provided to support the adequacy of the proposed training program.
3. The proposed REMS does not require training for those DATA-2000 waived physician who oversee the implantation and removal procedures. Therefore, the DATA-2000 waived physician may not have the necessary training to intervene during the procedure or manage complications after the procedure.

4. The closed distribution system does not conform to the requirements included in Title 21 United States Code Controlled Substances Act (CSA). The CSA defines "dispense" in Section 802 (Definitions) as the following:

> *to deliver a controlled substance to an ultimate user or research subject by, or pursuant to the lawful order of, a practitioner, including the prescribing and administering of a controlled substance and the packaging, labeling or compounding necessary to prepare the substance for such delivery.*

Therefore, if Probuphine is dispensed from a pharmacy, the medication would need to be provided directly to the patient (ultimate user) and could not be mailed to the DATA-2000 waived physician.

6 CONCLUSION

The Sponsor has proposed a REMS designed to provide training to HCPs for the implantation and removal procedure of Probuphine and to establish a closed distribution system. The Agency has identified several concerns with the Sponsor's proposed REMS. The details of the committee's discussion concerning these matters will be considered in the final design of the REMS, should Probuphine be approved.

Guidance for Industry

Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Kathleen Frost 301-796-2380, or (CBER) the Office of Communication, Outreach, and Development (OCOD) at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2009
Drug Safety

Guidance for Industry

Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

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U.S. Department of Health and Human Services
Food and Drug Administration
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September 2009
Drug Safety

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Guidance for Industry[1]
Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry on:

- The format and content of a proposed risk evaluation and mitigation strategy (REMS), including REMS supporting documentation;
- The content of assessments and proposed modifications of approved REMS;
- What identifiers to use on REMS documents; and
- How to communicate with FDA about a REMS.

This guidance applies to certain drug and biological products submitted for approval or approved under sections 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), or section 351 of the Public Health Service Act (PHS Act), that are required by FDA to have a REMS. The information on the content of a proposed REMS submission (section III of this document) also applies to proposed REMS that are voluntarily submitted by applicants or holders of approved applications (see section II.A of this document).

This guidance will address REMS elements and provisions that are broadly applicable to proposed REMS and to assessments and modifications of approved REMS. Other provisions, such as those that pertain only to abbreviated new drug applications (ANDAs), or expanded information about REMS assessments and proposed modifications, will not be fully addressed, but will be the subject of future guidance.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the FDAAA Title IX Working Group in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. FDAAA and REMS: Initial Approval and Postapproval Requirements

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85).[2] Title IX, Subtitle A, section 901 of this statute created new section 505-1 of the FDCA, which authorizes FDA to require persons submitting certain applications (applicants) to submit a proposed REMS as part of such application if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.[3] Section 505-1 applies to applications for approval of prescription drugs submitted under FDCA subsections 505(b) or (j) and applications submitted under section 351 of the Public Health Service Act. These applications are termed *covered applications* and refer to new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs). Please note that the term "drug" is used in this guidance to refer to prescription drug and biologic products for which there are pending or approved applications.

Section 505-1 also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS if the FDA becomes aware of new safety information as defined in 505-1(b)(3) and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug. Once the holder of an approved covered application is notified by FDA that a REMS is necessary, the holder must submit a proposed REMS within 120 days, or within such other reasonable time as FDA requires to protect the public health (section 505-1(a)(2)(B)).

In addition, persons with certain covered applications that were approved before the effective date of Subtitle A, March 25, 2008, were deemed to have in effect an approved REMS and were also required to submit a proposed REMS. See section II.C of this document, Products Deemed to Have in Effect an Approved REMS.

An applicant may voluntarily submit a proposed REMS without having been required to do so by FDA. For instance, without having been notified by FDA to submit a proposed REMS, an applicant may include a proposed REMS in an original application or in a supplemental application, or in an amendment to an existing original or supplemental application, if the applicant believes a REMS would be necessary to ensure that the benefits of the drug outweigh its risks and the other relevant statutory criteria in section 505-1 are met. Section V of this document describes submission types and document identification. If FDA determines that a

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[2] See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm.

[3] Subtitle A took effect on March 25, 2008, 180 days after enactment of FDAAA.

REMS is necessary to ensure that the benefits of the drug outweigh the risks, FDA will determine which elements of a REMS are necessary and will approve the REMS once the Agency has determined that the proposed REMS will ensure that the benefits of the drug outweigh the risks, and the other relevant statutory criteria in section 505-1 are met. An approved REMS that was voluntarily submitted is subject to the same requirements and enforcement as a REMS that was originally submitted as a required proposed REMS. If an applicant voluntarily submits a proposed REMS, it will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria. Proposed REMS that are not approved are not subject to the requirements and enforcement of an approved REMS. FDA will notify applicants who voluntarily submit a proposed REMS whether the REMS will be required. If the FDA determines that a REMS is not required, an applicant may undertake voluntary risk management measures that would be performed outside of a REMS.

B. Relationship Between REMS and RiskMAPs

Before FDAAA was enacted, FDA approved a small number of drug and biological products with risk minimization action plans (RiskMAPs). A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required safety reporting. For the majority of approved products, labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits. In a small number of cases, when additional measures were needed to ensure that the benefits of a drug outweigh the risks of the drug, FDA approved the drug with a RiskMAP. In 2005, FDA issued a guidance for industry on *Development and Use of Risk Minimization Action Plans*[4] (the RiskMAP guidance), that described how to develop RiskMAPs, select tools to minimize risks, evaluate and monitor RiskMAPs and monitoring tools, and communicate with FDA about RiskMAPs.

Now that FDAAA has given FDA the authority to require REMS when necessary to ensure that the benefits of a drug outweigh the risks, FDA anticipates that:

- A product that would previously have been approved with a RiskMAP will, instead, be approved with a REMS if statutory requirements for a REMS are met.[5]
- Products that would previously have been approved with a Medication Guide or patient package insert that meet the statutory requirements for a REMS will now be required to have a REMS.
- While certain products approved with RiskMAPs that included certain types of risk management tools have been deemed to have in effect an approved REMS (see section II.C of this document), all other approved RiskMAPs and approved Medication Guides and patient package inserts that were in place when Subtitle A took effect will continue to be in effect, unless they are replaced by or included in a REMS. They will be

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf
[5] Unless it is an ANDA based on a reference listed drug with an approved RiskMAP.

replaced by or included in a REMS if FDA determines, based on new safety information identified after approval of the product, that a REMS is necessary to ensure that the benefits of the drug outweigh the risks.

- ANDAs for which the reference listed drug has an approved RiskMAP will be approved with a comparable RiskMAP that includes the same essential elements.
- ANDAs for which the reference listed drug has a REMS will be approved with the elements of that REMS applicable to ANDAs.
- Revisions of existing Medication Guides or patient package inserts that meet REMS requirements will be approved as part of a REMS.

Many of the principles that were included in the RiskMAP guidance are embodied in the FDAAA REMS provisions as implemented by FDA. Many of those principles pertaining to REMS are included in this guidance, and others will be included in future guidance documents related to REMS. The RiskMAP guidance continues to apply to products with existing RiskMAPs (e.g., products with RiskMAPs that were not deemed to have in effect an approved REMS) and to products with new RiskMAPs (e.g., ANDAs for which the reference listed drug has a RiskMAP).

C. Products Deemed to Have in Effect an Approved REMS

Section 909(b)(1) of FDAAA addresses products approved before the effective date of Subtitle A that have been deemed to have in effect an approved REMS.

> A drug that was approved before the effective date of this Act is . . . deemed to have in effect an approved risk evaluation and mitigation strategy under section 505-1 of the Federal Food, Drug, and Cosmetic Act . . . if there are in effect on the effective date of this Act elements to assure safe use—
>
> (A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or
>
> (B) otherwise agreed to by the applicant and the Secretary for such drug.

Section 909(b)(2) states that the REMS for a drug deemed to have an approved REMS consists of the timetable required under section 505-1(d) and any additional elements under subsections 505-1(e) and (f) in effect for the drug on the effective date of FDAAA.

Section 909(b)(3) of FDAAA states:

> Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect . . . shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505-1 of the Act as if included in such application at the time of submission of the application to the Secretary.[6]

[6] 121 Stat. 951.

On March 27, 2008, FDA published in the *Federal Register* a list of drugs that were identified as deemed to have an approved REMS, and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008.[7] For most of these drugs, the elements of the existing RiskMAPs or restricted distribution and risk management programs were or will be simply converted to the new content and format of a REMS in the proposed REMS. FDA generally does not intend to make substantial changes to these programs during this conversion unless new safety or effectiveness information identified since the drug was approved (including an evaluation of the program identifying deficiencies) suggests that the existing REMS should be modified to ensure that the benefits of the product outweigh the risks. In those cases, FDA has or will require modifications to the REMS.

D. Content of a REMS

A REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS (505-1(d)). In addition, a REMS may include any or all of the other REMS elements, if specified criteria are met. These additional elements are listed below and described in more detail in section III of this document:

1. Timetable for Submission of Assessments

Section 505-1(d) requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. FDAAA specifies that the timetable for submission of assessments of the REMS must include an assessment by the dates that are 18 months and 3 years after the strategy is approved, and an assessment in the 7th year after the strategy is approved, or at another frequency specified in the strategy (see section III.A.6 of this document for additional information).

2. Additional Potential Elements

Section 505-1(e) lists "Additional Potential Elements" of a REMS that may include the following (see section III.A.3 of this document for additional information):

- A Medication Guide as provided for under part 208 of title 21, Code of Federal Regulations
- A patient package insert if such insert may help mitigate a serious risk of the drug
- A communication plan to health care providers if the plan may support implementation of an element of the strategy

3. Elements to Ensure Safe Use (ETASU)

[7] See *Federal Register* Notice "Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007" (73 FR 16313, March 27, 2008).

Section 505-1(f)[8] lists certain *Elements to Assure Safe Use* that may be required if the drug has been shown to be effective, but is associated with a serious adverse event and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate the specific serious risk(s) listed in the labeling of the product. Elements to assure safe use may be required for approved products when an assessment and Medication Guide, patient package insert, or communication plan are not sufficient to mitigate these risks. The elements to assure safe use must include one or more goals to mitigate the specific serious risk(s). If a REMS includes certain elements to assure safe use, the REMS may also include required implementation systems to enable the applicant to monitor, evaluate, and improve the implementation of the elements (see section III.A.4 of this document for additional information).

This guidance document uses the word *tool* to describe a process or system designed to implement one or more REMS elements. In some cases, an element itself, such as a Medication Guide, may be viewed as a tool. In other cases, such as for an ETASU that requires that a drug be dispensed to patients with evidence or other documentation of safe-use conditions (505-1(f)(3)(D)), specific tools are used to implement a REMS element; for example, systems to ensure that certain laboratory test result outcomes are obtained before a drug may be dispensed.

E. Assessments and Modifications of Approved REMS

FDAAA includes provisions for the assessment and modification of an approved REMS in section 505-1(g). Additional information on assessments and modifications is included in sections III.B.4 and IV of this document.

1. Voluntary Assessments and Proposed Modifications (505-1(g)(1) and (4))

In addition to required assessments of an approved REMS described below, an applicant may voluntarily submit an assessment of, and propose modifications to, an approved REMS at any time. Proposed modifications may enhance or reduce the approved REMS, and may include additions to or modifications of the timetable for submission of assessments, including a proposal to eliminate assessments, and/or the addition, modification, or removal of a Medication Guide, patient package insert, communication plan or ETASUs.

2. Required assessments (505-1(g)(2))

REMS assessments are **required** under the following circumstances:

- When submitting a supplemental application for a new indication for use, unless the approved REMS for the drug includes only a timetable for submission of assessments. FDA anticipates rarely requiring a REMS that includes only a timetable for submission of assessments.

[8] FDA is considering the implications of section 505-1(f) on the restricted distribution provisions under 21 CFR 314 Subpart H (drugs) – 314.520, and 21 CFR 601 Subpart E (biologics) – 601.42 and will address this in a future guidance.

- When required by the approved REMS, as provided for in the timetable for submission of assessments
- When required by the FDA, within a time period to be determined by the FDA, if the FDA determines that new safety or effectiveness information indicates that the timetable for submission of assessments should be modified and/or that a Medication Guide, patient package insert, communication plan, or ETASUs should be added, modified, or removed
- Within 15 days when ordered by the FDA, if the FDA determines that there may be a cause for withdrawal or suspension of approval under section 505(e) of the FDCA

F. REMS Are Enforceable

REMS required under section 505-1 are subject to inspection and are enforceable under the FDCA as amended by FDAAA.[9] A drug is misbranded under section 502(y) if the responsible person for that drug[10] fails to comply with a requirement of the approved strategy. Also, under section 303(f)(4)(A) of the FDCA, a responsible person who violates a REMS requirement is subject to civil monetary penalties of up to $250,000 per violation, not to exceed $1 million in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the responsible person of the violation. The penalties double for the second 30-day period, and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million per proceeding. In imposing a monetary penalty, FDA will consider the responsible person's efforts to correct the violation. In addition, under 505(p), a person may not introduce or deliver for introduction into interstate commerce an approved drug that is the subject of a covered application, if a REMS is required with respect to that drug, and the person fails to maintain compliance with the requirements of the approved REMS or with other requirements under 505-1, such as requirements regarding assessments of approved REMS.

III. CONTENT OF A PROPOSED REMS SUBMISSION TO FDA

A proposed REMS submission to FDA should include two parts: a *proposed REMS*, which is a concise document that describes the proposed goals and elements of the REMS and, once approved, will be the basis for enforcement; and a *REMS supporting document*, that expands on information included in the proposed REMS and provides additional information not included in the proposed REMS, including a thorough explanation of the rationale for, and supporting information about, the content of the proposed REMS. These two parts of a proposed REMS submission are described below.

A. Content of the Proposed REMS

The proposed REMS should include concise information describing the goal(s) of the REMS and the REMS element(s) proposed for inclusion in the approved REMS for the specified product.

[9] See FDAAA Title IX, section 902.

[10] The term 'responsible person' means the person submitting a covered application or the holder of the approved such application. Section 505-1(b)(7).

All proposed materials that are included as part of the REMS (e.g., proposed communication and education materials, Medication Guide, patient package insert, enrollment forms, prescriber and patient agreements) should be appended to the proposed REMS. The proposed REMS should be written to clearly describe the responsibilities of the applicant in implementing the REMS; for example, statements will generally begin with, "[Name of the applicant] will…" The proposed REMS should include the date by which each of the REMS elements will be implemented.

A template for the proposed REMS is available on the FDA's "Postmarket Drug Safety Information for Patients and Providers" Web site, at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm. Attachment A provides an example of a completed proposed REMS for a fictitious product that an applicant would submit to FDA for review. The preferred template may be periodically updated as we gain more experience with REMS; therefore, applicants should check the Web site for the latest version. Questions should be directed to the FDA contacts described in section V.C of this document.

Prior to approving a REMS, FDA may require applicants to revise a proposed REMS to ensure that the benefits of the drug will outweigh the risks.

FDA will append any REMS materials that will be included in the approved REMS, as described above, to the final REMS. The final REMS and appended documents will be referenced in and appended to the approval letter for the application or supplement that contains the proposed REMS, and the approval letter and appended documents will be posted on the following FDA Web sites:

For products regulated by CDER:

- The Drugs@FDA Web site at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
- The Postmarket Drug Safety Information for Patients and Providers Web site (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm). This Web site also includes a list of approved REMS (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm). The list of approved REMS includes links to the REMS document and REMS materials, excluding Medication Guides.
- Medication Guides can be accessed on the Drugs@FDA Web site and on the Postmarket Drug Safety Information for Patients and Providers Web site through the link to approved Medication Guides (http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm).

For products regulated by CBER:

- The Biologics Products and Establishments Web site at http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm
- The Postmarket Drug Safety Information for Patients and Providers Web site (see link above)

The elements of an approved REMS are enforceable under FDAAA, Title IX, section 902 (see section II.F of this document), and any changes to the REMS, including to the appended documents, must be submitted as a proposed modification of an approved REMS and approved by FDA before being implemented (see section IV).

The proposed REMS should contain the following sections as appropriate to manage the risks of the particular product; if an applicant is not proposing one of the elements, the proposed REMS should include a statement that the element is not necessary.

1. Product and Contact Information

The proposed REMS should include the application number, proprietary and established names, dosage form of the product, the drug class as described in the product's label, and the applicant's name and address. The proposed REMS should also include contact information, including position titles, for those responsible for the REMS policy, management, and implementation.

2. Goals

All REMS should include a statement of one or more overall goals. In addition, if the REMS has one or more elements to assure safe use (505-1(f)), the REMS must include one or more goals to mitigate a serious risk listed in the labeling of the drug for which the ETASUs are required. Even when ETASUs are not part of a REMS (e.g., a REMS with a Medication Guide or communication plan only), the goals of the REMS should be identified. Assessments of approved REMS should measure whether the goals are being met.

As used in this document, a proposed REMS goal is the desired safety-related health outcome or the understanding by patients and/or health care providers of the serious risks targeted by the use of specified REMS elements. REMS goals should target the achievement of particular health outcomes or knowledge related to known safety risks and should be stated in a way that aims to achieve maximum risk reduction. The following are examples of REMS goals: "Patients taking W drug should be aware of the serious risks relative to the potential benefits," "Patients on X drug should not also be prescribed Y drug," or "Fetal exposures to Z drug should not occur." Goals should be stated in absolute terms. Although it might not be possible to ensure that the goal can be met for every patient (i.e., no one on X drug receives Y drug), FDA believes that a goal, as the term implies, is a statement of the ideal outcome of a REMS.

REMS goals should be associated with pragmatic, specific, and measurable program objectives that result in processes or behaviors leading to achievement of the REMS goals. Objectives can be thought of as intermediate steps to achieving the overall REMS goal. A REMS goal can be associated with more than one objective, depending upon the frequency, type, and severity of the specific risk or risks being minimized. For example, a goal may be the elimination of occurrences of a serious adverse event caused by an interaction of the drug with another drug. The objectives could include lowering physician co-prescribing rates and/or pharmacist co-dispensing rates for the specific drugs.

3. Additional Potential REMS Elements

(a) Medication Guide and/or Patient Package Insert

As one element of a REMS, the FDA may require the development of a Medication Guide, as provided for under 21 CFR part 208, which sets forth requirements for patient labeling for human prescription drug products, including biological products, that the FDA determines pose a serious and significant public health concern requiring the distribution of FDA-approved patient information. Medication Guides will be required if the FDA determines that one or more of the following circumstances exist:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Under 21 CFR part 208 and in accordance with 505-1 of the FDCA, the applicant is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed the drug. This section of the REMS should describe the mechanisms the applicant intends to use for distribution of the Medication Guide.

In addition, FDA may require a patient package insert as part of a REMS if the FDA determines that the patient package insert may help mitigate a serious risk of the drug. Having both a required patient package insert and a Medication Guide for the same drug is not expected to occur frequently. In most instances, FDA anticipates requiring a Medication Guide (or requiring conversion of an existing PPI to a Medication Guide) if FDA is requiring patient labeling that meets Medication Guide requirements.

The following types of changes to a PPI would **not** ordinarily trigger the need to convert a PPI to a Medication Guide:

- Editorial changes
- Changes related to how to use a product (e.g., how to inject the product subcutaneously) *unless* these changes have the potential to mitigate a serious risk, such as overdose

Copies of Medication Guides and patient package inserts that are part of a REMS should be appended to the proposed REMS.

(b) Communication Plan

FDA may determine that a communication plan targeted at health care providers is a necessary element of a REMS if it may support implementation of the REMS. The communication plan may include sending letters to health care providers; disseminating information about REMS elements to encourage implementation by health care providers or to explain certain safety protocols, such as medical monitoring by periodic laboratory tests; or disseminating information to health care providers through professional societies about any serious risks of the drug and any protocol to assure safe use (section 505-1(e)(3)).

Copies of communication plan materials should be appended to the proposed REMS.

If an NDA has been approved with a REMS with a communication plan, and subsequently an abbreviated new drug application (ANDA) is approved with that NDA product as the reference listed drug, then FDA must undertake the communication plan (section 505-1(i)(2)(A)). Neither the holder of the NDA that is the reference listed drug nor the ANDA holder has to undertake a communication plan once an ANDA is approved. However, many tools that have previously been considered part of a communication plan, such as training materials, specified procedures, patient/physician agreements or other informed consent, patient educational materials, safety protocols, medical monitoring procedures, and data collection forms may fit under one or more elements to assure safe use (ETASU) if specified criteria are met. Both NDA holders and ANDA holders are required to implement ETASUs.

4. Elements to Assure Safe Use

Elements to assure safe use are intended to provide safe access for patients to drugs with known serious risks that would otherwise be unavailable. Required ETASUs are put in place to mitigate a specific serious risk listed in the labeling of a drug. Before requiring one or more ETASUs, the FDA must make the following determinations (505-1(f)(1)):

- That the drug, which has been shown to be effective but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements were required; and
- That for a drug initially approved without ETASUs, other possible elements of a REMS are not sufficient to mitigate such serious risk.

This subsection of the proposed REMS should describe the ETASUs included in the proposed REMS and any tools designed to implement one or more elements to assure safe use. Copies of all relevant materials should be appended to the proposed REMS. Examples of relevant materials include health care provider attestations; pharmacy, practitioner, health care setting, and patient enrollment forms; training materials; specified procedures; patient/physician agreements or other informed consent; patient educational materials; safety protocols; medical monitoring procedures; and data collection forms.

The following lists the elements to assure safe use that may be included in the REMS. Note that some of the tools designed to implement the elements to assure safe use may appear in more than one category:

A. Health care providers who prescribe the drug have particular training or experience, or are specially certified.

In general, section 505-1(f)(3)(A) pertains to prescribers of the drug. Elements under this category might require certification of training, or attestation of specific experience or knowledge, before the health care provider is enrolled in a program that allows that provider to prescribe the product.

For example, in order to be certified, a health care provider may be required to demonstrate that he or she:

- Can diagnose the condition for which the product is indicated
- Understands the risks and benefits of the product and has read the educational materials for prescribers
- Can diagnose and treat potential adverse reactions associated with the product

The program may require periodic recertification and reenrollment.

The opportunity to obtain this training or certification must be available to any willing provider, for example through an on-line or mail course, at reasonable cost to the provider (505-1(f)(3)(A)).

B. Pharmacies, practitioners, or health care settings that dispense the drug are specially certified.

In general, section 505-1(f)(3)(B) pertains to how the drug is dispensed. Elements under this category might require certification of training or attestation of specific experience or knowledge before the pharmacy, practitioner, or health care setting is enrolled in a program that allows the practitioner or staff at the pharmacy or health care setting to dispense the product.

For example, to be certified, practitioners and staff at pharmacies, hospitals, and infusion sites may be required to demonstrate that they:

- Understand the risks and benefits of the product and have read the educational materials before the drug is dispensed
- Agree to fill a prescription and dispense the drug only after receiving prior authorization
- Agree to check laboratory values, or check for the presence of stickers that providers affix to prescriptions for specified products to indicate that the patient has met all criteria for receiving the product (“qualification stickers”), before dispensing a drug
- Agree to fill a prescription and dispense the drug only within a specified period of time after the prescription is written
- Agree to fill prescriptions only from enrolled prescribers

The program may require periodic recertification and reenrollment.

The opportunity to obtain this certification must be available to any willing provider (505-1(f)(3)(B)).

C. The drug be dispensed to patients only in certain health care settings, such as hospitals.

In general, section 505-1(f)(3)(C) pertains to restrictions on dispensing the product to patients in specific health care settings.

For example, the applicant may be required to

- Ensure the drug is dispensed only to patients in hospitals that have met certain conditions
- Ensure the drug is dispensed only to physicians' offices equipped to treat the potential risks associated with the drug following administration of the drug (e.g., access to medication and equipment necessary to treat a serious allergic reaction)

D. The drug be dispensed only to patients with evidence or other documentation of safe-use conditions, such as laboratory test results.

In general, section 505-1(f)(3)(D) pertains to ensuring that patients meet specified criteria before drug exposure.

For example, evidence or other documentation of safe use conditions may include the following:

- Patients have been counseled about the risks and benefits of the product and have signed an acknowledgment that they understand the risks and benefits of the product
- Patients have been provided a copy of patient educational materials and demonstrated that they understand the risks and benefits of the product
- Patients receive drug only after specified authorization is obtained and verified by the pharmacy. Examples of authorizations include checking laboratory values and checking for physician qualification (stickers) on the prescription

E. Each patient using the drug be subject to certain monitoring.

Elements under 505-1(f)(3)(E) might require that patients be monitored or that specific follow-up should occur at specific time points.

Examples include the following:

- Patients' laboratory tests are monitored on a specified periodic basis to prevent the serious risk
- Patients are required to contact the prescriber within a specified period of time after beginning treatment with the drug to ensure they are still appropriate candidates for treatment
- Patients are required to contact their prescriber periodically during and following treatment to ensure they did not experience the serious risk associated with the use of the drug

F. Each patient using the drug be enrolled in a registry.

In general, section 505-1(f)(3)(F) pertains to enrolling patients into a program as part of an overall strategy to mitigate a specific serious risk listed in the labeling of the drug. The use of a registry may be combined with other ETASUs, such as when a registry is used to document that the drug is dispensed to patients with evidence or other documentation of safe-use conditions; or to document that each patient using the drug is subject to certain monitoring.

Drug access may be contingent on patient enrollment. The types of information that may be collected on enrolled patients include:

- Information on clinical outcomes
- Clinical and laboratory data
- Safety information
- Data on compliance with prescribed management and prescribing protocols
- Data on the impact of tools on ensuring compliance and outcomes

Registries that are established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required under a REMS. Registries may also serve as a repository for clinical data and allow for case finding and follow-up. These registries are not considered PMRs, but studies conducted using the data may be.[11]

5. Implementation System

Section 505-1(f)(4) of the FDCA gives the FDA authority to require an implementation system for a REMS that includes the ETASUs described under 505-1(f)(3)(B), (C), and (D). Through the implementation system, the applicant may be expected to take reasonable steps to monitor and evaluate implementation by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing those elements, and to work to improve their implementation.

[11] See the draft guidance for industry on *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act*, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

FDA may require the implementation system to include a description of how applicable products will be distributed. In addition, as part of the implementation system, FDA may require the certification of wholesalers and/or distributors who distribute the product to ensure that the product is distributed only to certified or otherwise specified pharmacies, practitioners, or health care settings that dispense the drug, or only to patients who meet the requirements of the REMS.

Other examples of methods used to monitor and evaluate implementation of REMS with ETASUs described under 505-1(f)(3)(B), (C), and (D) include the following:

- The applicant maintains a validated and secure database of all certified entities (pharmacies, practitioners, and health care settings) to ensure any certification requirements or other requirements for pharmacies, practitioners, or health care settings are met
- The applicant conducts periodic audits of pharmacies, practitioners, and health care settings to ensure compliance with ETASUs (e.g., documentation of safe-use conditions prior to dispensing drug)
- If the ETASUs include limits on where and how a drug may be dispensed, the applicant conducts periodic audits of wholesale shipment or distribution systems to determine that the drug is only being distributed to authorized entities

6. Timetable for Submission of Assessment of the REMS

This subsection of the proposed REMS should describe the proposed timetable for submission of assessments of the REMS as required by section 505-1(d) of the FDCA. REMS for NDAs and BLAs must include a timetable for submission of assessments of the REMS. REMS for ANDAs do not include a timetable for submission of assessments. Additional information on REMS and ANDAs will be included in future guidance.

Under section 505-1(d), each timetable for submission of assessments of a REMS must at a minimum include assessments submitted by 18 months and by 3 years after the REMS is initially approved, and in the 7th year after the REMS is initially approved, with additional dates if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. Factors that may influence the need for more frequent assessments of the REMS include, among others, the estimated size of the population likely to use the drug, the seriousness of known or potential risks that may be related to the drug, and knowledge about the effectiveness of REMS elements to mitigate the risks. The requirements for the assessments submitted by 18 months and by 3 years may be met through assessments submitted at specified earlier dates; for example, assessments required in an approved REMS to be submitted at 12 months and 24 months would meet the requirements for the assessments submitted by 18 months and 3 years.

The timetable specifies when the assessment will be submitted to FDA, not when the assessment will be performed. This subsection should specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an

assessment that is to be submitted by July 31 should conclude no earlier than June 1. The assessment is to be received by the FDA on or before the due date.

Requests for modification of the timetable for submission of assessments, including eliminating assessments, may be made after approval of the REMS (see 505-1(g)(4)). After the assessment due by 3 years after the REMS is initially approved is submitted, all further assessments, including the 7th-year assessment, may be eliminated if the FDA determines that serious risks of the drug have been adequately identified and assessed and are being adequately managed.

B. Content of the REMS Supporting Document

The REMS supporting document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS. A template for the REMS supporting document is available on the FDA's "Postmarket Drug Safety Information for Patients and Providers" Web site, at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm. The REMS supporting document should include the sections listed in the template for the applicable proposed REMS elements for the specified product, as well as a table of contents. The REMS supporting document should include a description of how and when each REMS element will be implemented and should specify the rationale for the overall timelines and milestones. If any REMS activity will not be implemented at the time of REMS approval, the REMS supporting document should include the rationale for the implementation schedule. For example, the document should address the rationale for whether a communication plan would be implemented before, or concurrently with, other elements. Additional information on each section of the REMS supporting document is described below.

1. Background

The Background section of the REMS supporting document should explain why a REMS is necessary and provide a concise summary of how the proposed REMS would ensure that the benefits of the drug outweigh the risks. For a new REMS that is proposed for an already-approved product, the Background section should also include the description of the new safety information that suggests a REMS is necessary.

The Background section should describe what is known about the risk to be minimized by the REMS, including the magnitude, severity, and frequency of the adverse events, whether there are particular populations at risk, the background incidence of the risk in the population likely to use the product, whether the adverse event can be prevented or is reversible, and the benefits that would be preserved by the implementation of the REMS. It should also describe the factors that FDA considers when determining whether a REMS is necessary to ensure that the benefits of the drug outweigh the risks: the estimated size of the population likely to use the product, the seriousness of the disease or condition that is to be treated with the product, the expected benefit of the product with respect to such disease or condition, the expected or actual duration of treatment with the drug, the risks and benefits of alternative therapies, and whether the drug is a new molecular entity. The statute specifically requires these factors to be considered for REMS

required at initial approval (505-1(a)(1)), but FDA will also consider these factors in making determinations about postapproval REMS.

The Background section of the REMS supporting document should include a discussion, if pertinent, about the successes and failures of actions by regulatory authorities, systems of health care, or applicants in mitigating the risks of concern for this product or similar products. Information on risk management plans submitted to other regulators, such as the European Union's EU Risk Management Plan,[12] should be included, with a clear description of how that information supports the proposed REMS, along with reasons for any differences between the proposed REMS and other risk management plans for the product.

Information provided by the applicant regarding relevant past experiences, domestically or in other countries, will assist in the development of REMS that are compatible with established distribution, procurement, and dispensing systems within the health care delivery system, and that avoid the cost of implementing REMS tools already determined to be unsuccessful. In addition, we encourage applicants to provide applicable information or evaluations from past experiences with products or programs that are similar to the proposed REMS. Brief descriptions of the available evidence regarding the effectiveness of each element and tool included in the proposed REMS may be mentioned in the Background section. Thorough descriptions should be included in the "Supporting Information on Proposed REMS Elements" section.

2. Goals Section

This section of the REMS supporting document should describe the rationale for the proposed goals of the REMS and summarize how each proposed element and stated objectives will individually and collectively contribute to achieving the goals. All REMS should include a statement of one or more overall goals. In addition, if the REMS has one or more elements to assure safe use (505-1(f)), the REMS must include one or more goals to mitigate a serious risk listed in the labeling of the drug for which the elements to assure safe use are required. Even if a REMS does not contain elements to assure safe use (e.g., a REMS that includes a Medication Guide or communication plan only), the goals of the REMS should be identified. Additional information about how each particular element and tool will contribute to achieving the goals of the REMS should be included in the "Supporting Information About Proposed REMS Elements" section described immediately below. REMS goals are described in more detail in section III.A.2 of this document.

3. Supporting Information About Proposed REMS Elements

This section should include a description of why particular elements and tools were chosen for the proposed REMS and how each particular element and tool will contribute to achieving the goals of the REMS. Each subsection about elements included in the proposed REMS should include a thorough description of the element(s) proposed for mitigating the risk or risks targeted by the proposed REMS; any tools proposed to be implemented under each element; how the

[12] GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL PRODUCTS FOR HUMAN USE, Doc. Ref. EMEA/CHMP/96268/2005 http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf.

elements or tools will mitigate the risk; how the elements or tools conform with elements or tools for other products with similar risks; and whether the elements or tools are compatible with established distribution, procurement, and dispensing systems.

A thorough description of the available evidence regarding the effectiveness of each element or tool should be provided, including, where applicable, results from pretesting of proposed elements or tools or a time frame for when these will be submitted. These subsections should also note whether the applicant sought input from patient or health care interests, and if so, a description of the feedback received regarding the feasibility of its REMS.

Elements to Assure Safe Use. Section 505-1(f)(2) requires that FDA consider how to ensure access and minimize the burden of a REMS that includes ETASUs. Therefore, for a proposed REMS that includes ETASUs, the Elements to Assure Safe Use subsection of the REMS supporting document should include the following:

- An explanation of how the proposed ETASUs correspond to the specific serious risks listed in the labeling
- An explanation of how the proposed ETASUs will mitigate the observed serious risk
- Verification that the proposed elements are not unduly burdensome on patient access to the drug considering the risk being mitigated. Include particular consideration of patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care.
- A description of how, to the extent practicable, the proposed ETASUs will minimize the burden on the health care delivery system: how the proposed ETASUs conform to those required for other drugs with similar serious risks, and how the proposed elements are designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

Implementation System. This subsection should include the rationale and supporting information for the proposed implementation system, including each method used to monitor and evaluate implementation of the REMS and any planned ways to improve its implementation.

Timetable for Submission of Assessments of the REMS. This subsection should include the rationale and supporting information for the proposed timetable for submission of assessments of the REMS. This subsection should also include the rationale for the interval that each assessment will cover and for the planned date the assessment will be submitted to the FDA.

4. REMS Assessment Plan

This section should describe the rationale and supporting information for the proposed plan to assess the REMS. Section 505-1(g) of the FDCA describes the requirements for REMS assessments. REMS assessments should include an evaluation of the extent to which each of the REMS elements are meeting the goals and objectives of the REMS, and whether or not the goals, objectives, or REMS elements should be modified. Plans to obtain this information should be included in the REMS supporting document to ensure that sufficient information will be collected to do a valid assessment of the REMS.

In accordance with section 505-1(g)(3)(A), for a REMS that includes one or more ETASUs, the REMS assessment shall include an assessment of the extent to which the ETASUs are meeting the goal (see section III.A.2), or whether the goal or such elements should be modified.

This subsection should describe the proposed REMS assessment plan, including the following:

- The proposed evaluation methods (including measurements or measures) for assessing the overall effectiveness of the REMS and the effectiveness of each of the REMS elements and tools (e.g., claims-based data systems, surveys, registries) and the rationales for the chosen measures.
- Targeted values for each measure and the timeframe for achieving them. Include interpretations of expected results under best- and worst-case scenarios. In addition, this section should specify what values of measures at specific time points will trigger consideration of REMS modification.
- The type of data that will be collected, and the nature and timing of data collection, analyses, audits, or monitoring that will be used to assess the performance of each individual REMS element or tool in achieving the REMS's objectives and goals.
- Where applicable and possible, this section should discuss plans to assess unintended and/or unfavorable consequences of the REMS following implementation.

For example, a REMS may indicate that the following data will be collected to support an assessment:

- A survey to evaluate knowledge of a labeled serious adverse event to determine whether patients are using the product correctly to prevent the adverse event, or to evaluate use of the product as labeled, particularly when the indicated use is for a restricted population or when numerous contraindications exist.

- Information about use patterns of the drug including:
    - Use by prescriber specialty
    - Patient-level data (age, gender, race)
    - Length of therapy
    - Indication

- Population-based administrative or claims-based data that capture service or payment claims to measure rates of specified serious adverse events.

- Active surveillance using sentinel reporting sites to determine rates of specified serious adverse events.

Whenever possible, specific assessment instruments (e.g., surveys) and methodology should be included in the REMS supporting document. If the assessment instruments and methodology are not available when the proposed REMS is submitted to FDA, at least 90 days before the assessments will be conducted, the applicant should update the REMS supporting document to include specific assessment instrument and methodology information. Updates to the REMS

supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions of the REMS, or updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. See section V.B.3 for information on how to identify the submission that includes specific assessment instruments when they are submitted after the REMS is approved.

For a REMS that includes a Medication Guide, information needed for assessment of the REMS should include but may not be limited to the following:

(a) Survey of patients' understanding of the serious risks of the drug
(b) Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
(c) Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If a product is distributed in unit-of-use packaging that includes a Medication Guide with a quantity of product dispensed to a single patient and not divided, the reports in (b) and (c) above would not be necessary.

This subsection of the REMS supporting document might also include information describing the rationale for, and a description of, all elements proposed to be included in the assessments of the REMS, such as the following:

- Narrative summary and analysis of serious adverse events of interest
- Summary of data that will be tracked in a REMS-related database
- Summary of wholesaler shipment data
- Summary of surveys conducted
- Summary of data on drug use
- Summary of registry data
- Refill frequency and amount

The assessment should include sufficient detail to identify the need for changes to the REMS. For example, an applicant may be required to assess reports of adverse events associated with the effectiveness of the REMS, each known occurrence of prescriptions written by health care providers who do not have required certification, or dispensing of the product by a pharmacy, practitioner, or health care setting that does not have the required certification. The assessment should also describe any corrective actions taken for these occurrences.

Requirements for Information on the Status of Any Postapproval Study or Clinical Trial Required Under Section 505(o) or Otherwise Undertaken to Investigate a Safety Issue

In accordance with section 505-1(g)(3)(B) and (C), all REMS assessments shall include certain information about any postapproval study or clinical trial required under section 505(o) or otherwise undertaken by the applicant to investigate a safety issue.

- For *postapproval studies*, the REMS assessment shall include the status of each study, including whether any difficulties completing the study have been encountered.
- For *postapproval clinical trials,* the REMS assessment shall include
  (a) The status of each clinical trial, including whether enrollment has begun,
  (b) The number of participants enrolled,
  (c) The expected completion date,
  (d) Whether any difficulties completing the clinical trial have been encountered, and
  (e) Registration information with respect to registry and results databank requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. This includes information on whether the data have been submitted to clinicaltrials.gov, and proper certifications have been submitted to the FDA.

The REMS assessment can satisfy the requirements in section 505-1(g)(3)(B) and (C), for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue, by referring to relevant information included in the most recent annual report required under section 506B of the FDCA and 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70, and including any updates to the status information since the annual report was prepared, as long as the information required about postapproval studies and clinical trials described above was provided in the annual report. Failure to submit a complete REMS assessment under 505-1(g)(3) could result in enforcement action.

5. Other Relevant Information

This subsection should include information on the positions within the applicant's company responsible for REMS policy, management, and implementation, including organizational chart(s) that include these REMS-related positions.

In addition, this subsection should include any other information relevant to the proposed REMS not included elsewhere.

C. Foreign Language REMS

Foreign-language versions of REMS, including any materials appended to the REMS such as Medication Guides, patient package inserts, communication and education materials, enrollment forms, prescriber and patient agreements, and others, are not considered part of the approved REMS. FDA will not review foreign-language versions of REMS.

Consistent with CDER's approach to foreign-language labeling, when applicants distribute foreign-language versions of a currently approved REMS, they are responsible for ensuring that such materials are complete and accurate.[13] Supplemental applications for foreign-language REMS are not required and should not be submitted.

[13] Note that applicants are required to comply with the requirements regarding distribution of labels and labeling under 21 CFR 201.15(c).

IV. REMS ASSESSMENT AND PROPOSED REMS MODIFICATION SUBMISSIONS TO FDA

REMS assessments must be submitted according to the timetable for submission of assessments included in the REMS, and as otherwise required (see section II.E of this document and 505-1(g)). Applicants may also voluntarily submit an assessment of, and propose a modification to, an approved REMS at any time. An applicant's proposal for modification of an approved REMS must include an assessment of the REMS.

Under section 505-1(g)(2)(C), when FDA determines that new safety information indicates that an element of the REMS, such as a Medication Guide, should be modified, the application holder is required to assess the REMS. Where the application holder agrees with the Agency's proposed modification to a REMS that consists solely of a Medication Guide and/or a communication plan, that assessment may consist of a statement that the Medication Guide and/or communication plan would be adequate with the proposed modifications to achieve its/their purpose.

Proposed modifications may include an enhancement or reduction to the approved REMS, and may include additions or modifications to the timetable for submission of assessments, including a proposal to eliminate assessments (after the 3-year period described in 505-1(d)), and/or the addition, modification, or removal of a Medication Guide, patient package insert, communication plan, or ETASU.

A proposed modification of an approved REMS that is not associated with an existing supplemental application should be submitted as a new prior-approval supplemental application as described in section V of this document.

Any proposed modification to the approved REMS, including any proposed changes to materials that are included as part of the REMS (e.g., communication and education materials, enrollment forms, prescriber and patient agreements), must be submitted as a proposed modification to an approved REMS in a new prior-approval supplemental application, as described in section V of this document, and must not be implemented until the modified REMS is approved by FDA.

Each proposed modification submission should include a new proposed REMS (based on the proposed REMS template described in section III.A) that shows the complete previously approved REMS with all proposed modifications highlighted. In addition, the submission should include an update to the REMS supporting document that includes the rationale for and description of all proposed modifications and any impact the proposed modifications would have on other REMS elements. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions of the REMS, or updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. The content of the proposed REMS and REMS supporting document are described in section III of this document. Additional information on assessments and modifications to approved REMS is included in section II.E of this document. More complete information on assessments and modifications of approved REMS will be the subject of future guidance.

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965
966 **V. COMMUNICATING WITH FDA REGARDING REMS**
967
968 **A. Submission Type**
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970 A proposed REMS may be included in the initial submission of an original or supplemental
971 application, or may be submitted as an amendment to an existing original or supplemental
972 application. All supplemental applications that include a proposed REMS or proposed
973 modifications to an approved REMS should be submitted as prior-approval supplements, not as
974 changes being effected supplements (see 21 CFR 314.70 and 601.12).
975
976 A proposed REMS submitted after approval and not associated with an existing supplemental
977 application should be submitted as a new supplemental application.
978
979 Assessments of approved REMS may be submitted voluntarily at any time and must be
980 submitted as required in the timetable for submission of assessments of the REMS and as
981 otherwise required (see sections II.E and IV of this document). A REMS assessment alone (i.e.,
982 not proposing a modification) is not considered a supplemental application.
983
984 REMS assessments that include a proposed modification to the approved REMS should be
985 submitted either as a new supplemental application or included in a related supplemental
986 application. They can be included in a related supplemental application either at the time of
987 submission or as an amendment to the supplemental application.
988
989 A supplemental application for a new indication for use for a product with an approved REMS
990 must include a REMS assessment unless the drug is not subject to section 503(b) and the REMS
991 for the drug includes only the timetable for submission of assessments (505-1(g)(2)(A)). The
992 supplemental application for the new indication should include the required REMS assessment
993 and may propose modifications to the REMS.
994
995 A proposed REMS and proposed modifications to an approved REMS should be submitted using
996 the format in the template for a proposed REMS described in section III.A, and, to facilitate the
997 review process, the submission should include electronic versions of the proposed REMS or
998 proposed modifications to an approved REMS as an Adobe Acrobat pdf document and in a
999 document generated using a word processing program.
1000
1001 As described in section III.C, supplements for foreign-language REMS are not required and
1002 should not be submitted.
1003
1004 Send requests for current information on where REMS-related documents should be included
1005 when submitted as part of an electronic common technical document (eCTD) and questions
1006 about electronic submissions to FDA to the following email address: esub@fda.hhs.gov.
1007
1008 **B. Document Identification**
1009

1. Proposed REMS

Regardless of when or how a proposed REMS is submitted, it is critical to provide identifying information on the submitted REMS document so that it can be tracked, routed, and reviewed appropriately. In each case, the first page of the submission should prominently identify the submission as providing a **PROPOSED REMS** in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

When the proposed REMS is submitted as part of an original application:

NEW ORIGINAL APPLICATION FOR <name of drug>
PROPOSED REMS

When the original proposed REMS is submitted as an amendment to an existing original or supplemental application:

NDA/BLA/ANDA [assigned #]
PROPOSED REMS

NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]
PROPOSED REMS

When the original proposed REMS is submitted postapproval as a new supplemental application:

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
PROPOSED REMS

When the original proposed REMS is submitted postapproval with a new supplemental application:

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
< other applicable content identification >
PROPOSED REMS

On the first page of subsequent submissions related to an already-submitted proposed REMS, prominently identify the submission by including this wording in bold capital letters at the top of the letter:

NDA/BLA/ANDA [assigned #]
PROPOSED REMS-AMENDMENT

NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]
PROPOSED REMS-AMENDMENT

2. Assessments and Modifications of Approved REMS

On the first page of the submission of an assessment of an approved REMS, prominently identify its content in bold capital letters at the top of the page:

NDA/BLA/ANDA [assigned #]
REMS ASSESSMENT

If a REMS assessment is submitted as a part of another submission, it is critical to provide complete identifying information on the submission so that it can be tracked, routed, and reviewed appropriately. In each case, the first page of the submission should prominently identify the submission as providing a **REMS ASSESSMENT** in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification.

The first page of the submission of an assessment of an approved REMS submitted with a supplemental application for a new indication for use should prominently identify the content in bold capital letters at the top of the page. The submission may include proposed modifications to the approved REMS. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
< other supplement identification >
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

The first page of the submission of proposed modifications to an approved REMS submitted as a stand-alone new supplemental application or included with another new supplemental application should prominently identify the content in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
< other supplement identification >
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

The first page of the submission of proposed modifications to an approved REMS submitted as an amendment to a pending supplemental application should prominently identify the content in bold capital letters at the top of the page:

NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

The first page of subsequent submissions related to a proposed modification to an approved REMS should prominently identify the submission by including this wording in bold capital letters at the top of the page:

NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]
PROPOSED REMS MODIFICATION -AMENDMENT

3. Other REMS Submissions

An applicant may submit REMS submissions that are not proposed REMS, proposed modifications to an approved REMS, amendments to proposed REMS, proposed modifications to an approved REMS, or REMS assessments. Such submissions may include a request for information about what to include in a proposed REMS, information about the REMS assessment plan for an approved REMS (e.g., assessment instruments and methodology), general correspondence about an approved REMS that does not include a proposed modification, amendment to a proposed modification, or a REMS assessment, or other submissions that do not fall into the categories described above. On the first page of such submissions, prominently identify its content with the words, "**REMS - OTHER**" followed by a concise description of the content in bold capital letters at the top of the page. For example:

NDA/BLA/ANDA [assigned #]
REMS-OTHER
SURVEY METHODOLOGY

The first page of a submission requesting Agency input on the content of a proposed REMS that has **not** yet been submitted should include the following wording in bold capital letters at the top of the page:

NDA/BLA/ANDA [assigned #]
REMS-OTHER
REQUEST FOR GUIDANCE ON CONTENT OF PROPOSED REMS

If the proposed REMS has already been submitted, such a request should be identified as a proposed REMS amendment – see section V.B.1.

C. Questions about REMS

In the Center for Drug Evaluation and Research (CDER), the primary contact about a proposed REMS for a product under an NDA or BLA is the regulatory project manager in the Office of New Drugs (OND) review division assigned to that product. The primary contact about a proposed REMS for a product under an ANDA is the Director of the Division of Labeling and Program Support in the Office of Generic Drugs (OGD). The Office of Surveillance and Epidemiology, and other program offices as needed, will work with OND and OGD in the review and development of a proposed REMS.

In the Center for Biologics Evaluation and Research (CBER), the primary contact about a proposed REMS is the regulatory project manager in the office with product responsibility. The Office of Biostatistics and Epidemiology, and other program offices as needed, will work with the product office in the review and development of a proposed REMS.

GLOSSARY – applicable to terms as used in this document

Assessment: An assessment of the approved REMS as described in section II.E and III.B.4 of this document.

Changes Being Effected Supplement: Also called a "changes being effected supplemental application." A supplement that includes changes that do not require supplement submission and approval prior to the changes being implemented; the application holder may commence distribution of the drug product involved upon receipt by the agency of a supplement for these changes. A "Changes Being Effected in 30 days" supplement includes changes that do not require approval prior to the changes being implemented, but requires supplement submission at least 30 days prior to distribution of the drug product made using the change. If, after review, FDA disapproves a changes being effected supplement or a changes being effected in 30 days supplement, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change (21 CFR 314.70(c) and 601.12(c)). See section V.A of this document.

Goal: The desired safety-related health outcome or the understanding of serious risks targeted by the use of specified REMS elements. See section III.A.2 of this document.

Objective: An intermediate step to achieving the overall goals of the REMS. Objectives should be pragmatic, specific, and measurable. Objectives may use one or more elements or tools that result in processes or behaviors leading to achievement of the REMS goals. A REMS goal can be translated into different objectives, depending upon the frequency, type, and severity of the specific risk or risks being minimized. See section III.A.2 of this document.

Prior-approval Supplement: Also called a "prior-approval supplemental application." A supplemental application that includes changes requiring supplement submission and approval prior to the distribution of the product made using the change. (21 CFR 314.70(b) and 601.12(c)). See section V.A of this document.

Qualification Stickers: Stickers given by the applicant to providers to affix to prescriptions for specified products to indicate that the patient has met all criteria for receiving the product.

REMS: Stands for "Risk Evaluation and Mitigation Strategy," and is the enforceable document that describes the elements that an applicant is required to implement. See section III.A of this document.

REMS Supporting Document: A document that includes a thorough explanation of the rationale and supporting information for the content of the proposed REMS. See section III.B of this document.

Tool: A process or system designed to implement one or more REMS elements. In some cases an element itself, such as a Medication Guide, may be viewed as a tool. In other cases, such as for an ETASU that requires that a drug be dispensed to patients with evidence or other documentation of safe-use conditions (505-1(f)(3)(C)), specific tools are used to implement a

REMS element. Examples of such tools include systems that ensure certain laboratory test result outcomes are obtained before a drug may be dispensed.

ATTACHMENT A: EXAMPLE OF A REMS DOCUMENT FOR A FICTITIOUS DRUG

NDA ##-### Drug X

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Class of Product as per label

ABCD Pharmaceuticals

123 Fake Street
City, State Zip
Contact Information for those responsible for
REMS policy, management, and implementation

(555)-xxx-xxxx
www.emailaddress.xxx

I. GOAL

To minimize the risk of drug exposure during pregnancy in women of child-bearing potential taking Drug X. Because Drug X is teratogenic, ABCD Pharmaceuticals (ABCD) will mitigate this risk by:

- Ensuring that only females of childbearing potential with a negative pregnancy test begin therapy with Drug X and only females of childbearing potential with a monthly negative pregnancy test continue therapy with Drug X.
- Ensuring that females of childbearing potential understand the risks to the fetus and know what precautions are necessary to prevent pregnancy.
- Ensuring that all patients and health care providers understand the risks associated with Drug X.

This drug is contraindicated in female patients who are or may become pregnant.

II. REMS ELEMENTS

A. Medication Guide (FDCA Section 505-1(e)(2))

A Medication Guide will be dispensed with each Drug X prescription. To ensure compliance with 21 CFR 208.24, ABCD will attach a Drug X Medication Guide to each unit-of-use package of Drug X to ensure that the Medication Guide is given to each patient with each new prescription and refill. A copy of the Medication Guide is appended to the REMS Document. The Medication Guide will be available on the ABCD Web site within 10 days of approval of the Medication Guide.

B. Communication Plan (FDCA Section 505-1(e)(3))

ABCD will implement a communication plan to health care providers to support implementation of this REMS:

1. The audience for this communication plan is health care professionals (HCPs)—especially neurologists, endocrinologists, and pharmacists.

2. ABCD will provide physicians and pharmacists with educational materials listed below that describe the key risks and benefits of Drug X:

   a. Prescriber Materials — Dear Health Care Professional Letter
   b. Pharmacist Materials — Dear Pharmacist Letter
   c. Additional Resources — Drug X REMS Program Internet Site

   The printed communication and educational materials listed above are appended.

3. Distribution of materials: Communication plan materials will be distributed within 60 days of approval of the Drug X REMS.

   a. At the time the Drug X REMS elements to assure safe use are implemented, ABCD will send the Dear Health Care Professional Letter by mass mailing to targeted Drug X prescribers to announce the REMS program and the requirements of the program. The mailing will include the materials listed in 2a above. Copies of these materials will be available through the product Web site.

   b. At the time the Drug X REMS elements to assure safe use are implemented, ABCD will send the Dear Pharmacist Letter by mass mailing to targeted pharmacies who currently order Drug X, to announce the REMS program and the requirements of the program. The mailing will include the materials listed in 2b above. Copies of these materials will be available through the product Web site.

C. Elements To Assure Safe Use (FDCA Section 505-1(f)(3))

ABCD will implement the following elements to ensure safe use to mitigate the risk of drug exposure during pregnancy by women of child-bearing potential. The elements to assure safe use will be implemented within 60 days of approval of the Drug X REMS.

1. Drug X will be prescribed only by prescribers who are specially certified under 505-1(f)(3)(A) by enrollment in the Drug X REMS program.

   a. ABCD will ensure that physicians and other appropriately licensed health care providers who prescribe Drug X are specially certified. ABCD will ensure that, to become certified, each prescriber, on the prescriber enrollment form, attests to the following:

- To have read and understood the communication and educational materials for prescribers regarding the risks and benefits of Drug X, including the Drug X Prescriber Guide and the Prescriber Contraception Counseling Guide
- To have knowledge of the high risk of severe birth defects associated with Drug X
- To know the risk factors for unplanned pregnancy and the effective measures to avoid pregnancy
- To prescribe Drug X after ensuring documentation of safe use conditions described below
- To submit information about any pregnancy they learn about to the pregnancy registry
- To monitor patients treated with Drug X as described below

b. ABCD will maintain a list of all certified prescribers and will provide the list to those needing to verify that a prescriber has obtained the required certification.

c. ABCD will ensure that prescribers will be recertified in the Drug X REMS program annually.

The following materials are part of the REMS and are appended:

- Prescriber enrollment form,
- Prescriber Guide
- Prescriber Contraception Counseling Guide

2. Drug X will be dispensed only by pharmacies that are specially certified under 505-1(f)(3)(B) by enrollment in the Drug X REMS program.

a. ABCD will ensure that responsible pharmacy personnel from pharmacies that dispense Drug X are specially certified. ABCD will ensure that, to be certified, responsible pharmacy personnel will attest to the following:

- To have read and understood the communication and educational materials for pharmacists regarding the risks and benefits of Drug X, including the Drug X Pharmacist Guide
- To have knowledge of the high risk of severe birth defects associated with Drug X
- To train all pharmacists to fill and dispense Drug X only after ensuring documentation of safe-use conditions described below
- To ensure that all pharmacists who fill and dispense Drug X comply with required documentation of safe-use conditions described below
- To agree not to sell, borrow, lend, or otherwise transfer Drug X to or from another pharmacy

b. ABCD maintains a list of all certified pharmacies and will provide the list to those needing to verify that a pharmacy has obtained the required certification.

c. Drug X will be distributed to certified pharmacies.

d. Pharmacies will be recertified in the Drug X REMS program annually.

The pharmacy enrollment form and Pharmacist Guide are part of the REMS and are appended.

3. Drug X will only be dispensed to patients with documentation of safe-use conditions under 505-1(f)(3)(D)) described below:

a. ABCD will ensure that prescribers of Drug X will:

- Register each patient in the Drug X REMS program (patient enrollment form is appended)
- Determine the childbearing status of all female patients
- Counsel each female of childbearing potential (FCBP) before beginning therapy with Drug X and on a monthly basis to avoid pregnancy by using effective contraceptive forms or refer the patient for contraception counseling
  - Provide them with the following educational materials: Guide for Patients Who *Can* Become Pregnant (appended)
  - Confirm that FCBP have signed the appropriate informed consents — Informed consent for Patients Who *Can* Become Pregnant (appended)
- Counsel males and females not of child bearing potential about the risks and benefits of Drug X before beginning therapy with Drug X.
  - Provide them with the following educational materials: Guide for Patients Who *Cannot* Become Pregnant (appended)
  - Confirm that males and females not of childbearing potential have signed the appropriate informed consents — Informed consent for Patients Who *Cannot* Become Pregnant (appended)
- Complete for each patient either the Drug X Prescriber Checklist for Patients Who *Can* Become Pregnant, or the Drug X Prescriber Checklist for Patients Who *Cannot* Become Pregnant (appended)
- For female patients of childbearing potential prior to each prescription:
  - Indicate patient's chosen contraceptive forms each month by telephone or secure Internet Web site
  - Order CLIA-certified pregnancy test for each patient prior to each prescription and enter results of pregnancy test each month by telephone or secure Internet Web site

b. ABCD will ensure that pharmacies that dispense Drug X will:

- Obtain authorization from the Drug X REMS program by telephone or secure Internet Web site for every Drug X prescription and write the authorization number on each prescription
- Dispense only a 30-day supply
- Dispense within 7 days of a last negative pregnancy test
- Dispense the Drug X Medication Guide with each prescription

c. ABCD will ensure that Drug X is dispensed only to patients who have met the following conditions:

- All patients have:
  - Signed the informed consent prior to beginning therapy with Drug X
- Females of childbearing potential (before each prescription) have:
  - Obtained a CLIA-certified pregnancy test
  - Indicated chosen contraceptive forms each month by telephone or secure Internet Web site
  - Completed a questionnaire each month through a secure Internet Web site

4. ABCD will ensure that patients who are treated with Drug X are monitored by their prescribers monthly for the duration of Drug X therapy and for 1 month following Drug X discontinuation under section 505-1(f)(3)(E). Monitoring will include the following elements:

- Re-counseling all patients about the risks and benefits of Drug X therapy and determining whether they are still appropriate for Drug X therapy
- Determining whether the childbearing status of female patients has changed
- Obtaining a CLIA-certified pregnancy test prior to each Drug X prescription
- Ensuring FCBP are still on appropriate contraception and re-counseling FCBP of the importance of complying with contraceptive methods during and for 1 month following therapy with Drug X

5. ABCD will ensure that Drug X will only be dispensed to patients who are enrolled in the REMS program registry under 505-1(f)(3)(F) and who meet the following conditions:

- Patient must understand that severe birth defects can occur with the use of Drug X by female patients.
- Patient must be reliable in understanding and carrying out instructions.
- Patient must agree to not share Drug X with anyone.
- Patient must agree to not donate blood while on Drug X and for 1 month after Drug X discontinuation.
- Females of child-bearing potential (FCBP) must:
  - Not be pregnant and understand the importance of avoidance of pregnancy
  - Be capable of following mandatory contraceptive measures

The following information will be collected on enrolled patients:

- Age, gender, and childbearing status
- Documentation of counseling
- Prescription data (e.g., dates RX filled, quantity dispensed)
- For FCBP:
  - Baseline and monthly pregnancy test (dates and results)
  - Chosen methods of contraception
- For females who become pregnant
  - Maternal and fetal outcomes
  - Information on circumstances that led to failure to prevent pregnancy

D. Implementation System (FDCA Section 505-1(f)(4))

The implementation system will include the following components:

1. ABCD will maintain a validated and secure database of all entities enrolled under 505-1(f)(3)(B) and (D) and 505-1(f)(4), including wholesalers/distributers, pharmacies and patients.
2. ABCD will ensure that wholesalers/distributers who distribute Drug X are specially certified. To become certified, wholesalers/distributers will be enrolled in the Drug X REMS program.

    a. The Drug X REMS Program wholesaler/distributor enrollment process is composed of the following three steps that must be completed prior to receiving Drug X inventory for distribution:

        i. The Distributor's Authorized Representative reviews the Wholesaler/Distributor Program Materials.

        ii. Prior to receiving Drug X, the Distributor's Authorized Representative completes and signs the Distributor Enrollment Form and faxes it to the Drug X REMS Program. In signing the Enrollment Form, the Representative is required to indicate they understand that Drug X is available only through the Drug X REMS Program, agree to comply with program requirements, and acknowledge that:

            A. I will ensure that relevant staff are trained about the Drug X REMS Program for Drug X procedures.

            B. I will ensure that relevant staff distribute Drug X only to Drug X REMS pharmacies that are active in the database.

            C. I will provide monthly records of Drug X shipments to each Drug X REMS pharmacy.

D. I will permit a program-related audit of our shipping records to corroborate that we are shipping Drug X only to Drug X REMS pharmacies.

iii. A Drug X REMS Program professional reviews the form, requests any missing or illegible information, and, when the form has been verified to be accurate and successfully completed, the distributor is notified of activation.

b. Upon initial activation, wholesalers/distributors remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

c. If a previously active wholesaler becomes inactive, the wholesaler/distributor can become active again by completing the standard wholesaler enrollment process in its entirety.

d. Wholesalers/distributors are re-educated and re-enrolled following substantial changes to the program or at least every 2 years. Substantial changes to the Drug X REMS Program are defined as changes that modify the operation of the Drug X REMS Program in a way that changes Drug X REMS Program procedures for distributors.

e. The Distributor Enrollment Form is part of the REMS and is appended.

3. ABCD will monitor wholesaler distribution data to ensure that only registered entities are dispensing Drug X.
4. ABCD will monitor pharmacies to ensure these entities are dispensing Drug X to patients only after receiving authorization.
5. ABCD will correct pharmacy noncompliance with program requirements.
6. ABCD will conduct periodic audits of registered pharmacies to determine whether the data collected is in the manner and frequency agreed upon with FDA.
7. ABCD will maintain a Call Center (1-800-ABCD411) to respond to questions from practitioners, pharmacists, and patients (FDAAA Section 505-1(f)(3)(B), and (D)).

E. **Timetable for Submission of Assessments**

ABCD will submit REMS Assessments to FDA every 6 months from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. ABCD will submit each assessment so that it will be received by the FDA on or before the due date.

[Attachments are not included in this example.]

Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction

A Treatment Improvement Protocol

TIP 40

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
www.samhsa.gov

BTP Buprenorphine Clinical Guide

Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction

Laura McNicholas, M.D., Ph.D.
Consensus Panel Chair

A Treatment Improvement Protocol

TIP 40

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Acknowledgments

Numerous people contributed to the development of this TIP (see pp. ix, xi, and appendix J). This publication was produced by the American Institutes for Research® (AIR) under the Center for Substance Abuse Treatment (CSAT) contract, task order number 277-00-6401 under the Substance Abuse and Mental Health Services Administration (SAMHSA) contract, Number 277-99-6400, U.S. Department of Health and Human Services (DHHS). CAPT Susanne Caviness, Ph.D., SR SURG Angel A. González, M.D., and Raymond Hylton, Jr., R.N., M.S.N., served as the CSAT Government Project Officers. Anton C. Bizzell, M.D., and Alan Trachtenberg, M.D., M.P.H., served as the CSAT Medical Editors. Christina Currier served as the CSAT TIPs Task Leader. Elizabeth F. Howell, M.D., served as the Senior Medical Editor. Wayne Brandes, D.O., M.P.H., served as the AIR Medical Editor and Project Director. Janet Carrese served as the AIR Deputy Project Director. Other AIR personnel included Susan Bratten, Senior Editor; Susan Keller, M.P.H., M.S., B.S.N., Quality Assurance Editor; and Patricia Louthian, Document Production Specialist. In addition, Center for Health Policy Studies (CHPS) Consulting staff Roy Walker, M.B.A., Kimberly Stern, M.H.A., Elly Gilbert, M.S., R.N., C.H.E.S., and Ji Kim served as the original support team for the consensus and field review panels. Writers were Margaret Boone, Ph.D.; Nancy J. Brown; Mary A. Moon; Deborah J. Schuman; Josephine Thomas, M.F.A.; and Denise L. Wright, Ph.D.

Disclaimer

The opinions expressed herein are the views of the consensus panel members and do not necessarily reflect the official position of CSAT, SAMHSA, or DHHS. No official support of or endorsement by CSAT, SAMHSA or DHHS for these opinions or for particular instruments, software, or resources described in this document are intended or should be inferred. The guidelines in this document should not be considered substitutes for individualized client care and treatment decisions.

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Recommended Citation

Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.

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DHHS Publication No. (SMA) 04-3939
Printed 2004

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What Is a TIP?

Treatment Improvement Protocols (TIPs) are best-practice guidelines for the treatment of substance use disorders, provided as a service of the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Center for Substance Abuse Treatment (CSAT). CSAT's Office of Evaluation, Scientific Analysis and Synthesis draws on the experience and knowledge of clinical, research, and administrative experts to produce the TIPs, which are distributed to a growing number of facilities and individuals across the country. As alcoholism and other substance use disorders are increasingly recognized as major problems, the audience for the TIPs is expanding beyond public and private substance use disorder treatment facilities.

After selecting a topic, CSAT invites staff from pertinent Federal agencies and national organizations to a resource panel that recommends specific areas of focus as well as resources that should be considered in developing the content of the TIP. Then recommendations are communicated to a consensus panel composed of experts who have been nominated by their peers. This panel participates in a series of discussions; the information and recommendations on which they reach consensus become the foundation of the TIP. The members of each consensus panel represent substance use disorder treatment programs, hospitals, community health centers, counseling programs, criminal justice and child welfare agencies, and private practitioners. A panel chair (or cochairs) ensures that the guidelines mirror the results of the group's collaboration.

A large and diverse group of experts reviews the draft document closely. The Buprenorphine Expert Panel, a distinguished group of substance abuse experts and professionals in such related fields as primary care, mental health, and social services, worked with the Consensus Panel Chair and the CSAT Division of Pharmacologic Therapies to generate new and updated changes to the subject matter for this TIP based on the field's current needs for information and guidance. Once the changes recommended by the field reviewers have

been incorporated, the TIP is prepared for publication in print and online.

The TIPs can be accessed via the Internet at http://www.kap.samhsa.gov/products/manuals/index.htm. The use of electronic media also means that the TIPs can be updated more easily so that they can continue to provide the field with state-of-the-art information. Although each TIP includes an evidence base for the practices its panel recommends, CSAT recognizes that the field of substance use disorder treatment is evolving continuously and that research frequently lags behind the innovations pioneered by those in the field. A major goal of each TIP is to convey "front line" information quickly but responsibly. For this reason, recommendations in the TIP are attributed either to panelists' clinical experience or to the appropriate literature. If there is research to support a particular approach, citations are provided.

This TIP, *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*, provides consensus- and evidence-based guidance on the use of buprenorphine, a new option for the treatment of opioid addiction. The goal of this TIP is to provide information that physicians can use to make practical and informed decisions about the use of buprenorphine to treat opioid addiction. The Guidelines address a number of topic areas related to this goal, including the physiology and pharmacology of opioids, opioid addiction, and treatment with buprenorphine; the screening and assessment of opioid addiction problems; detailed protocols for opioid addiction treatment with buprenorphine; management of special populations; and policies and procedures related to office-based opioid addiction treatment under the paradigm established by the Drug Addiction Treatment Act of 2000. This TIP represents another step by CSAT toward its goal of bringing national leaders together to improve substance use disorder treatment in the United States.

Other TIPs may be ordered by contacting the National Clearinghouse for Alcohol and Drug Information (NCADI), (800) 729-6686 or (301) 468-2600; TDD (for the hearing impaired), (800) 487-4889. See http://www.kap.samhsa.gov/products/manuals/index.htm.

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Foreword

Our Nation has made great strides in recent years in achieving recovery for persons with substance use disorders. We know much more about how to deliver recovery-oriented substance abuse treatment, improve service quality, achieve desired improvements in quality-of-life outcomes, and implement needed care systems in each community in the United States. Our vision is of a life in the community for everyone.

The Treatment Improvement Protocol (TIP) series promotes resilience and facilitates recovery from substance use disorders. The TIPs add to our knowledge base and provide best practice guidance to clinicians, program administrators, and payors. They are the result of careful consideration of all relevant clinical and health services research findings, demonstration experience, and implementation requirements. For each TIP topic, an expert panel of non-Federal clinical researchers, clinicians, program administrators, and patient advocates debates and discusses best practices until its members reach a consensus.

The talent, dedication, and hard work that TIPs panelists and reviewers bring to this highly participatory process have bridged the gap between the promise of research and the needs of practicing clinicians and administrators. We are grateful to all who have joined with us to contribute to advances in the substance use disorder treatment field.

We hope you will find many uses for the information contained in this volume and that you will join in our goal of helping all Americans with substance use disorders realize healthy, contributing lives in their communities nationwide.

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Executive Summary

Federal statute, the Drug Addiction Treatment Act of 2000 (DATA 2000), has established a new paradigm for the medication-assisted treatment of opioid addiction in the United States (Drug Addiction Treatment Act of 2000). Prior to the enactment of DATA 2000, the use of opioid medications to treat opioid addiction was permissible only in federally approved Opioid Treatment Programs (OTPs) (i.e., methadone clinics), and only with the Schedule II opioid medications methadone and levo-alpha-acetyl-methadol (LAAM), which could only be dispensed, not prescribed.* Now, under the provisions of DATA 2000, qualifying physicians in the medical office and other appropriate settings outside the OTP system may prescribe and/or dispense Schedule III, IV, and V opioid medications for the treatment of opioid addiction if such medications have been specifically approved by the Food and Drug Administration (FDA) for that indication. (The text of DATA 2000 can be viewed at http://www.buprenorphine.samhsa.gov/fulllaw.html.)

In October 2002, FDA approved two sublingual formulations of the Schedule III opioid partial agonist medication buprenorphine for the treatment of opioid addiction. These medications, Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone), are the first and, as of this writing, the only Schedule III, IV, or V medications to have received such FDA approval and, thus, to be eligible for use under DATA 2000. Office-based treatment with buprenorphine promises to bring opioid addiction care into the mainstream of medical practice, thereby greatly expanding access to treatment and bringing new hope to thousands.

DATA 2000 directs the Substance Abuse and Mental Health Services Administration (SAMHSA) to develop a Treatment Improvement

*Due to a number of factors, including the association of LAAM with cardiac arrhythmias in some patients, as of January 1, 2004, the sole manufacturer has ceased production of the drug.

Protocol (TIP) containing best practice guidelines for the treatment and maintenance of opioid-dependent patients. This TIP, *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*, is the product of that mandate. The TIP was developed by SAMHSA and a team of independent substance abuse treatment professionals, in consultation with the National Institute on Drug Abuse, the Drug Enforcement Administration (DEA), and FDA. The purpose of this TIP is to provide physicians with science-based clinical practice guidelines on the use of buprenorphine in the treatment of opioid addiction. The primary audience of this TIP is physicians who are interested in providing buprenorphine for the treatment of opioid addiction.

In developing this TIP, the consensus panel, made up of research and clinical experts in the field of opioid addiction treatment, recognized that while buprenorphine offers new hope to many individuals, pharmacotherapy alone is rarely sufficient for the long-term successful treatment of opioid addiction. As a result, these guidelines emphasize that optimally effective and comprehensive opioid addiction care is achieved when attention is provided to all of an individual's medical and psychosocial comorbidities.

This TIP is composed of 6 chapters and 10 appendices, including a complete list of references (Appendix A, Bibliography). Chapter 1, Introduction, describes the basic facts regarding opioid addiction, the traditional approaches to its treatment, and the new DATA 2000 treatment paradigm.

Chapter 2, Pharmacology, addresses, in-depth, the physiology and pharmacology of opioids in general, and of buprenorphine in particular. The chapter also provides a review of the research literature regarding the safety and effectiveness of buprenorphine for the treatment of opioid addiction.

Chapter 3, Patient Assessment, summarizes an approach to screening and assessment of individuals who are addicted to opioids and who may be candidates for treatment with buprenorphine.

Chapter 4, Treatment Protocols, provides detailed protocols on the use of buprenorphine for the treatment of opioid addiction, including both maintenance and withdrawal treatment approaches.

Chapter 5, Special Populations, discusses several special populations whose circumstances require careful consideration as they begin buprenorphine treatment. Treating these special populations requires an understanding of available resources and often involves collaboration with specialists in other areas of care.

Chapter 6, Policies and Procedures, discusses legal and regulatory issues pertaining to the provision of opioid addiction treatment, including the procedures and physician qualifications necessary to obtain the required waiver under DATA 2000 to provide office-based opioid addiction treatment, recommended office practice policies and procedures, the security and confidentiality of opioid addiction care information, and the use of buprenorphine in OTPs.

The following sections summarize the content of this TIP and are grouped by chapter.

Chapter 1, Introduction

Chapter 1 provides an overview of opioid addiction in the United States today, including the historical context of the current treatment environment, the scope of the opioid addiction problem, the traditional approaches to treatment, and an introduction to buprenorphine as an opioid addiction treatment.

Opioid addiction includes not only misuse and abuse of heroin, but also the less commonly recognized issue of misuse and abuse of prescription opioid pain medications, such as hydrocodone, oxycodone, and meperidine.

Rates of addiction to prescription opioids have been increasing. The incidence of emergency department visits related to prescription opioid pain medications has more than doubled between 1994 and 2001. Recent data show that in at least 15 metropolitan areas, two or more narcotic pain medications—primarily oxycodone, hydrocodone, and codeine—were ranked among the 10 most common drugs involved in drug abuse deaths (SAMHSA 2002*b*).

The prevalence of heroin addiction in the United States also has been increasing and currently is believed to be the highest it has been since the 1970s. According to the Office of National Drug Control Policy (ONDCP), an estimated 810,000 to 1,000,000 individuals in the United States were addicted to heroin in the year 2000 (ONDCP 2003).

Well-run methadone maintenance programs (with programming that includes counseling services, vocational resources, referrals, and appropriate drug monitoring) have been shown to decrease opioid use and related crime, increase employment, and decrease the incidence of human immunodeficiency virus (HIV) related to needle sharing. In addition, treatment in such programs improves physical and mental health and decreases overall mortality from opioid addiction. Unfortunately, despite these results, methadone maintenance treatment system capacity has not kept pace with the rise in the prevalence of opioid addiction.

More than 20 years ago, buprenorphine was identified as a viable option for the maintenance treatment of individuals addicted to opioids. Research conducted over the past two decades has documented the safety and effectiveness of buprenorphine for this indication. The enactment of DATA 2000 has now enabled physicians in the United States to offer specifically approved forms of buprenorphine for the treatment of opioid addiction.

Chapter 2, Pharmacology

Buprenorphine has unique pharmacological properties that make it an effective and well-tolerated addition to the available pharmacological treatments for opioid addiction. This chapter reviews the general pharmacology of opioid agonists and antagonists, as well as the opioid *partial agonist* properties of buprenorphine.

Drugs that activate opioid receptors on neurons are termed opioid *agonists*. Heroin and methadone are opioid agonists. The repeated administration of opioid agonists results in dose-dependent physical dependence and tolerance. *Physical dependence* is manifested as a characteristic set of withdrawal signs and symptoms upon reduction, cessation, or loss of an active compound at its receptors. *Addiction*, conversely, is a *behavioral* syndrome characterized by the repeated, compulsive seeking or use of a substance, despite adverse social, psychological, and/or physical consequences. Opioid addiction often, but not always, is accompanied by tolerance, physical dependence, and opioid withdrawal symptoms.

Opioids that bind to opioid receptors but block them, rather than activating them, are termed opioid *antagonists*. Examples of opioid antagonists are naltrexone and naloxone.

Opioid *partial agonists* are drugs that activate receptors, but not to the same degree as full agonists. Increasing the dose of a partial agonist does not produce as great an effect as does increasing the dose of a full agonist. The agonist effects of a partial agonist reach a ceiling at moderate doses and do not increase from that point, even with increases in dosage. *Buprenorphine is an opioid partial agonist*. It is the partial agonist properties of buprenorphine that make it a safe and an effective option for the treatment of opioid addiction. Buprenorphine has sufficient agonist properties such that when it is administered to individuals who are not opioid dependent but

who are familiar with the effects of opioids, they experience subjectively positive opioid effects. These subjective effects aid in maintaining compliance with buprenorphine dosing in patients who are opioid dependent.

Buprenorphine occupies opioid receptors with great affinity and thus blocks opioid full agonists from exerting their effects. Buprenorphine dissociates from opioid receptors at a slow rate. This enables daily or less frequent dosing of buprenorphine, as infrequently as three times per week in some studies.

Buprenorphine is abusable, consistent with its agonist action at opioid receptors. Its abuse potential, however, is lower in comparison with that of opioid full agonists. A formulation containing buprenorphine in combination with naloxone has been developed to decrease the potential for abuse via the injection route. Physicians who prescribe or dispense buprenorphine or buprenorphine/naloxone should monitor for diversion of the medications.

Due to the potential for serious drug–drug interactions, buprenorphine must be used cautiously with certain other types of medications, particularly benzodiazepines, other sedative drugs, opioid antagonists, medications metabolized by the cytochrome P450 3A4 system, and opioid agonists.

Chapter 3, Patient Assessment

This chapter provides an approach to the screening, assessment, and diagnosis of opioid addiction problems, and for determining when buprenorphine is an appropriate option for treatment. The necessary first steps in the medical management of opioid addiction are (1) the use of validated screening tools to identify patients who may have an opioid use problem and (2) further assessment to clearly delineate the scope of an opioid addiction problem when one is identified. When treatment is indicated, consideration must be given to the appropriate treatment approach, treatment setting, and level of treatment intensity, based on a patient's preferences, addiction history, presence of medical or psychiatric comorbidities, and readiness to change. Buprenorphine is a treatment option for many, but not for all.

Screening

The Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction Consensus Panel recommends that physicians periodically and regularly screen *all* patients for substance use and substance-related problems, not just those patients who fit the stereotypical picture of addiction. Several validated addiction screening instruments are discussed. The full text of selected screening instruments is provided in Appendix B, Assessment and Screening Instruments.

Assessment

If screening indicates the presence of an opioid use disorder, further assessment is indicated to thoroughly delineate the patient's problem, to identify comorbid or complicating medical or emotional conditions, and to determine the appropriate treatment setting and level of treatment intensity for the patient. Complete assessment may require several office visits, but initial treatment should not be delayed during this period.

The Guidelines document provides recommendations on effective interviewing techniques and on the components of the complete history, physical examination, and recommended initial laboratory evaluation of patients with opioid addiction.

The consensus panel recommends that initial and ongoing drug screening should be used to detect or confirm the recent use of drugs (e.g., alcohol, benzodiazepines, barbiturates), which could complicate patient management. Urine screening is the most commonly used and generally most cost-effective testing method.

Diagnosis of Opioid-Related Disorders

After a thorough assessment of a patient has been conducted, a formal diagnosis can be made. As a general rule, to be considered for buprenorphine maintenance, patients should have a diagnosis of *opioid dependence*, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000). This diagnosis is based not merely on physical dependence on opioids but rather on opioid addiction with compulsive use despite harm. (See DSM-IV-TR diagnostic criteria in Appendix C, DSM-IV-TR Material.)

Determining Appropriateness for Buprenorphine Treatment

A detailed approach to determining the suitability of buprenorphine as a treatment option for patients with opioid addiction is included in the Guidelines. The evaluation includes determining if appropriate patient motivation exists and ruling out contraindicating medical and psychiatric comorbidities.

Patients for whom buprenorphine may be an appropriate treatment option are those who

- Are interested in treatment for opioid addiction
- Have no contraindications to buprenorphine treatment
- Can be expected to be reasonably compliant with such treatment
- Understand the benefits and risks of buprenorphine treatment
- Are willing to follow safety precautions for buprenorphine treatment
- Agree to buprenorphine treatment after a review of treatment options

Patients less likely to be appropriate candidates for buprenorphine treatment of opioid addiction *in an office-based setting* are individuals whose circumstances or conditions include

- Comorbid dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol)
- Significant untreated psychiatric comorbidity
- Active or chronic suicidal or homicidal ideation or attempts
- Multiple previous treatments for drug abuse with frequent relapses (except that multiple previous *detoxification* attempts followed by relapse are a strong indication for long-term *maintenance* treatment)
- Poor response to previous treatment attempts with buprenorphine
- Significant medical complications

Chapter 4, Treatment Protocols

This chapter provides detailed protocols for the use of buprenorphine in the treatment of opioid addiction. A variety of clinical scenarios are addressed, including whether patients are addicted to long- versus short-acting opioids, and whether the approach selected is maintenance treatment or medically supervised withdrawal (which **must** be followed by long-term drug-free or naltrexone treatment to be useful to the patient).

Maintenance Treatment

Maintenance treatment with buprenorphine for opioid addiction consists of three phases: (1) induction, (2) stabilization, and (3) maintenance. Induction is the first stage of buprenorphine treatment and involves helping patients begin the process of switching from the opioid of abuse to buprenorphine. The goal of the induction phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no

withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. The consensus panel recommends that the buprenorphine/naloxone combination be used for induction treatment (and for stabilization and maintenance) for most patients. The consensus panel further recommends that initial induction doses be administered as observed treatment; further doses may be provided via prescription thereafter.

To minimize the chances of precipitated withdrawal, patients who are transferring from long-acting opioids (e.g., methadone, sustained release morphine, sustained release oxycodone) to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine/naloxone soon thereafter. Because of the potential for naloxone to precipitate withdrawal in both mother and fetus, pregnant women who are deemed to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy.

The stabilization phase has begun when a patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists. Dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance.

The longest period that a patient is on buprenorphine is the maintenance phase. This period may be indefinite. During the maintenance phase, attention must be focused on the psychosocial and family issues that have been identified during the course of treatment as contributing to a patient's addiction.

Medically Supervised Withdrawal ("Detoxification")

Buprenorphine can be used for the medically supervised withdrawal of patients from both self-administered opioids and from opioid agonist treatment with methadone or LAAM.

The goal of using buprenorphine for medically supervised withdrawal from opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms (and avoiding side effects of buprenorphine).

Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase. The consensus panel recommends that patients dependent on short-acting opioids (e.g., hydromorphone, oxycodone, heroin) who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine/naloxone tablets. The use of buprenorphine (either as buprenorphine monotherapy or buprenorphine/naloxone combination treatment) to taper off long-acting opioids should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and in coordination with patients' OTPs.

Nonpharmacological Interventions

Pharmacotherapy alone is rarely sufficient treatment for drug addiction. For most patients, drug abuse counseling—individual or group—and participation in self-help programs are necessary components of comprehensive addiction care. As part of training in the treatment of opioid addiction, physicians should at a minimum obtain some knowledge about the basic principles of brief intervention in case of relapse. Physicians considering providing opioid addiction care should ensure that they are capable of providing psychosocial services, either in their own practices or through referrals to reputable behavioral health practitioners in their communities. In fact, DATA 2000 stipulates that when physicians submit notification to SAMHSA to obtain the required waiver to practice opioid addiction treatment outside the OTP setting, they must attest to their capacity to refer such patients for appropriate counseling and other nonpharmacological therapies.

Treatment Monitoring

Patients and their physicians together need to reach agreement on the goals of treatment and develop a treatment plan based on the patient's particular problems and needs. During the stabilization phase, patients receiving maintenance treatment should be seen on at least a weekly basis. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, the physician may determine that less frequent visits (biweekly or longer, up to 30 days) are acceptable. During opioid addiction treatment with buprenorphine, toxicology tests for relevant illicit drugs should be administered at least monthly.

Chapter 5, Special Populations

This chapter discusses the approach to patients who have certain life circumstances or comorbid medical or behavioral conditions that warrant special consideration during the assessment and treatment of opioid addiction.

Patients With Medical Comorbidities

Patients who are addicted to opioids often have other medical comorbid problems as a consequence of both high-risk behaviors and of direct toxic effects of the active and inert ingredients in illicit drugs. In patients being treated with buprenorphine for opioid addiction, it is important to screen for and manage common comorbid medical conditions and to anticipate known and potential drug interactions.

Pregnant Women and Neonates

The scant evidence available does not show any causal adverse effects on pregnancy or neonatal outcomes from buprenorphine treatment, but this evidence is from case series, not from controlled studies. Methadone is currently the standard of care in the United States for the treatment of opioid addiction in pregnant women. Pregnant women who present for treatment of opioid addiction should be referred to specialized services in methadone maintenance treatment programs. If such specialized services are refused by a patient or are unavailable in the community, maintenance treatment with buprenorphine may be considered as an alternative.

Adolescents/Young Adults

Buprenorphine can be a useful option for the treatment of adolescents with opioid addiction problems. The treatment of addiction in adolescents, however, is complicated by a number of medical, legal, and ethical considerations. Physicians intending to treat addiction in adolescents should be thoroughly familiar with the laws in their States regarding parental consent. Physicians who do not specialize in the treatment of opioid addiction should strongly consider consulting with, or referring adolescent patients to, addiction specialists. Additionally, State child protection agencies can be a valuable resource when determining the proper disposition for adolescent patients addicted to opioids.

Geriatric Patients

Literature on the use of buprenorphine in geriatric patients is extremely limited. Due to potential differences in rates of metabolism and absorption compared to younger individuals, care should be exercised in the use of buprenorphine in geriatric patients.

Patients With Significant Psychiatric Comorbidity

The presence and severity of comorbid psychiatric conditions must be assessed prior to initiating buprenorphine treatment, and a

determination made whether referral to specialized behavioral health services is necessary. The psychiatric disorders most commonly encountered in patients addicted to opioids are other substance abuse disorders, depressive disorders, posttraumatic stress disorder, substance-induced psychiatric disorders, and antisocial and borderline personality disorder.

As with medical comorbidities, it is important to explore the medications used to treat the other psychiatric conditions. Assessing for drug interactions is a critical part of the process.

Polysubstance Abuse

Abuse of multiple drugs (polysubstance abuse) by individuals addicted to opioids is common. Pharmacotherapy with buprenorphine for opioid addiction will not necessarily have a beneficial effect on an individual's use of other drugs. Care in the prescribing of buprenorphine for patients who abuse alcohol and for those who abuse sedative/hypnotic drugs (especially benzodiazapines) must be exercised because of the documented potential for fatal interactions.

Patients With Pain

Physicians may encounter particular complexities with regard to abuse and addiction in the use of opioids to treat patients with pain. Some patients move from needing prescription opioids for the treatment of pain to abusing them. Physicians concerned about this changing diagnostic picture now may legally use an opioid—buprenorphine—to help facilitate a controlled detoxification in order to manage the physical dependence of the patient who no longer has pain that requires an opioid, but who continues to take the opioid for its mood-altering effects.

Patients who need treatment for pain *but not for addiction* should be treated within the context of a medical or surgical setting. They should not be transferred to an opioid maintenance treatment program simply because they have become physically dependent on prescribed opioids in the course of medical treatment.

Patients who *are* being treated for addiction also may experience pain due to illness or injury unrelated to drug use. Pain in patients receiving buprenorphine treatment for opioid addiction should be treated initially with nonopioid analgesics when appropriate.

Patients maintained on buprenorphine whose acute pain is not relieved by nonopioid medications should receive the usual aggressive pain management, which may include the use of short-acting opioid pain relievers. While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. When restarting buprenorphine, to prevent acutely precipitating withdrawal, administration generally should not begin until sufficient time has elapsed for the opioid pain medication to have cleared from the patient's system, as demonstrated by the onset of early withdrawal symptoms. Patients who are receiving long-acting opioids for chronic severe pain may not be good candidates for buprenorphine treatment because of the ceiling effect on buprenorphine's analgesic properties.

Patients Recently Discharged From Controlled Environments

A number of issues should be considered in determining the most appropriate treatment modalities for patients with addiction who are recently released from controlled environments (e.g., prison). Intensive buprenorphine monitoring activities are required, and treating physicians may be called upon to verify and explain treatment regimens (e.g., to parole and probation officers); to document patient compliance; and to interact with the legal system, employers, and others. If an OTP alternative is available, physicians

should determine if any patient factors preclude referral.

Healthcare Professionals Who Are Addicted to Opioids

There is a substantial problem of addiction to prescription opioids among physicians and other health professionals, especially within certain specialties. Prescription opioid addiction in health professionals should be viewed as an occupational hazard of the practice of medicine. Health professionals with substance abuse disorders often require specialized, extended care.

Chapter 6, Policies and Procedures

This chapter presents information on a number of administrative and regulatory issues pertaining to the use of controlled substances in the treatment of opioid addiction that are beyond the general medico-legal responsibilities that govern most other types of medical practice. Physicians should become thoroughly familiar with these issues prior to undertaking the treatment of opioid addiction.

The DATA 2000 Waiver

To practice office-based treatment of opioid addiction under the auspices of DATA 2000, physicians must first obtain a waiver from the special registration requirements established in the Narcotic Addict Treatment Act of 1974 and its enabling regulations. To obtain a DATA 2000 waiver, a physician must submit notification to SAMHSA of his or her intent to begin dispensing and/or prescribing this treatment. The Notification of Intent form must contain information on the physician's qualifying credentials and must contain additional certifications, including that the physician (or the physician's group practice) will not treat more than 30 patients for addiction at any one time. Notification of Intent forms can be filled out and submitted online at the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov. Alternatively, the form can be printed out from the site and submitted via ground mail or fax. (The site contains detailed information about buprenorphine, the DATA 2000 paradigm, and the physician waiver process.) Physicians who meet the qualifications defined in DATA 2000 are issued a waiver by SAMHSA and a special identification number by DEA.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications as defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to the necessary, concurrent psychosocial services. The consensus panel recommends that all physicians who plan to practice opioid addiction treatment with buprenorphine attend a DATA 2000-qualifying 8-hour training program on buprenorphine. SAMHSA maintains a list of upcoming DATA 2000-qualifying buprenorphine training sessions on the SAMHSA Buprenorphine Web site. Additional information about DATA 2000 and buprenorphine also can be obtained by contacting the SAMHSA Buprenorphine Information Center by phone at 866-BUP-CSAT (866-287-2728) or via e-mail at info@buprenorphine.samhsa.gov.

Preparing for Office-Based Opioid Treatment

Prior to embarking on the provision of office-based addiction treatment services, medical practices that will be new to this form of care should undertake certain preparations to ensure the highest quality experience for patients, providers, and staff. Providers and practice staff should have an appropriate level of training, experience, and comfort with opioid addiction treatment. Linkages with other medical and mental health professionals

should be established to ensure continuity of treatment and the availability of comprehensive, community-based, psychosocial services.

Privacy and Confidentiality

The privacy and confidentiality of individually identifiable drug or alcohol treatment information is protected by SAMHSA confidentiality regulation Title 42, Part 2 of the Code of Federal Regulations (42 C.F.R. Part 2). This regulation mandates that addiction treatment information in the possession of substance abuse treatment providers be handled with a greater degree of confidentiality than general medical information. Among other stipulations, regulation 42 C.F.R. Part 2 requires that physicians providing opioid addiction treatment obtain signed patient consent before disclosing individually identifiable addiction treatment information to any third party. The requirement for signed patient consent extends to activities such as telephoning or faxing addiction treatment prescriptions to pharmacies, as this information constitutes disclosure of the patient's addiction treatment. A sample consent form with all the elements required by 42 C.F.R. Part 2 is included as Appendix D, Consent to Release of Information Under 42 C.F.R. Part 2.

Buprenorphine Use in OTPs

In May 2003, the Federal OTP regulations (42 C.F.R. Part 8) were amended to add Subutex® and Suboxone® to the list of approved opioid medications that may be used in federally certified and registered OTPs (i.e., methadone clinics). OTPs that choose to use Subutex® and Suboxone® in the treatment of opioid addiction must adhere to the same Federal treatment standards established for all medications under 42 C.F.R. Part 8.

1 Introduction

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Summary and Overview of the Guidelines

Practical Guidelines for Physicians

Physicians are invited to use the *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* to make practical and informed decisions about the treatment of opioid addiction with buprenorphine. This document provides step-by-step guidance through the opioid addiction treatment decisionmaking process. Using the materials provided in these guidelines, physicians should be able to (1) perform initial screening and assessment of patients with opioid addiction, (2) determine the appropriateness of buprenorphine treatment for patients with opioid addiction, (3) provide treatment of opioid addiction with buprenorphine according to established protocols, (4) assess for the presence of and arrange appropriate treatment services for comorbid medical and psychosocial conditions, and (5) determine when to seek specialty addiction treatment referral or consultation.

The history of opioid addiction treatment forms an important backdrop for the decisions that physicians will make regarding their use of buprenorphine. Developing informed decisions about care should take into account the state of the art of opioid addiction treatment and ancillary services that exist to support both the patient and physician.

Historical Context

A significant breakthrough in the treatment of opioid addiction occurred with the introduction of methadone in the 1960s. Methadone maintenance proved safe and effective and enabled patients to lead functional lives—something that was often not possible using only drug-free approaches. Within a few years of its introduction, however, new laws and regulations in the United States, including the Methadone Regulations in 1972 and the Narcotic Addict Treatment Act of 1974, effectively limited methadone maintenance treatment to the context of the Opioid Treatment Program (OTP) (i.e., methadone clinic) setting. These laws and regulations established a closed distribution system for

methadone that required special licensing by both Federal and State authorities. The new system made it very difficult for physicians to use methadone to treat opioid addiction in an office setting or even in a general drug rehabilitation program. To receive methadone maintenance, patients were required to attend an OTP, usually on a daily basis. The stigma and inconvenience associated with receiving methadone maintenance in the OTP setting led, in part, to the current situation in the United States in which it is estimated that fewer than 25 percent of the individuals with opioid addiction receive any form of treatment for it (NIH Consensus Statement 1997). Another result of the closed distribution system was that most U.S. physicians were prevented from gaining experience and expertise in the treatment of opioid addiction. The Food and Drug Administration (FDA) approval of the longer acting opioid agonist levo-alpha-acetyl-methadol (LAAM) in the 1990s did little to change the situation.* (Additional information about substance abuse statistics and treatment availability in the United States can be found on the Substance Abuse and Mental Health Services Administration [SAMHSA] Office of Applied Studies [OAS] Web site at http://www.oas.samhsa.gov/).

The promise of DATA 2000 is to help destigmatize opioid addiction treatment and to enable qualified physicians to manage opioid addiction in their own practices…

Efforts to return opioid addiction treatment to the mainstream of medical care began to take shape and gain momentum in the 1990s. In October 2000, the Children's Health Act of 2000 (P.L. 106-310) was enacted into law. Title XXXV of the Act provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000; Clark 2003).

Under the provisions of DATA 2000, qualifying physicians may now obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. On October 8, 2002, two new sublingual formulations of the opioid partial agonist *buprenorphine*, Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone), became the first and, as of this writing, the only Schedule III, IV, or V medications to have received this FDA approval.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. (Chapter 6 provides a detailed discussion of the qualifying criteria defined in DATA 2000 and of the procedure for obtaining a waiver.)

Physicians who obtain DATA 2000 waivers may treat opioid addiction with Subutex® or Suboxone® in any appropriate clinical settings in which they are credentialed to practice medicine. The promise of DATA 2000 is to help destigmatize opioid addiction treatment and to enable qualified physicians to manage

*Due to a number of factors, including the association of LAAM with cardiac arrhythmias in some patients, as of January 1, 2004, the sole manufacturer has ceased production of the drug.

opioid addiction in their own practices, thus greatly expanding currently available treatment options and increasing the overall availability of treatment.

New Guidelines

The new guidelines provide information about the medical use of buprenorphine, based on (1) the evidence available from buprenorphine studies and (2) clinical experience using buprenorphine in the treatment of opioid addiction. The guidelines are as complete as the expert members of the Consensus Panel on Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction could make them and should provide a reasonable basis for current best practices in the area. Physicians should note that the guidelines are not intended to fully address all possible issues that can arise in the treatment of patients who are addicted to opioids. Some issues cannot be substantively addressed in the guidelines because of the lack of controlled studies and the limited U.S. experience using buprenorphine in office-based settings. Physicians are urged to seek the advice of knowledgeable addiction specialists if their questions are not answered fully by the guidelines, and should keep themselves aware of training and information on the use of buprenorphine that becomes available after the publication of this document. Such information will be posted regularly on the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov.

Opioid Addiction Today in the United States

Opioid Addiction

Opioid addiction is a neurobehavioral syndrome characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and/or physical consequences.

Addiction is often (but not always) accompanied by physical dependence, a withdrawal syndrome, and tolerance. *Physical dependence* is defined as a physiological state of adaptation to a substance, the absence of which produces symptoms and signs of withdrawal. *Withdrawal syndrome* consists of a predictable group of signs and symptoms resulting from abrupt removal of, or a rapid decrease in the regular dosage of, a psychoactive substance. The syndrome is often characterized by overactivity of the physiological functions that were suppressed by the drug and/or depression of the functions that were stimulated by the drug. *Tolerance* is a state in which a drug produces a diminishing biological or behavioral response; in other words, higher doses are needed to produce the same effect that the user experienced initially.

It is possible to be physically dependent on a drug without being addicted to it, and conversely, it is possible to be addicted without being physically dependent (Nelson et al. 1982). An example of physical dependence on opioids without addiction is a patient with cancer who becomes tolerant of and physically dependent on opioids prescribed to control pain. Such a patient may experience withdrawal symptoms with discontinuation of the usual dose but will not experience social, psychological, or physical harm from using the drug and would not seek out the drug if it were no longer needed for analgesia (Jacox et al. 1994). An example of addiction to opioids without physical dependence is a patient addicted to oxycodone who has been recently detoxified from the drug. In this situation, the patient may no longer be suffering from withdrawal symptoms or tolerance but may continue to crave an opioid high and will invariably relapse to active opioid abuse without further treatment.

Factors contributing to the development of opioid addiction include the reinforcing properties and availability of opioids, family and peer influences, sociocultural environment, personality, and existing psychiatric disorders. Genetic heritage appears to

influence susceptibility to alcohol addiction and, possibly, addiction to tobacco and other drugs as well (Goldstein 1994).

Addiction Rates

According to the January 2003 Drug Abuse Warning Network (DAWN) Report published by SAMHSA's OAS, the incidence of abuse of prescription opioid pain medications (also known as narcotic analgesics), such as hydrocodone, oxycodone, meperidine, and propoxyphene, has risen markedly in recent years (Crane 2003). The incidence of emergency department (ED) visits related to these medications has been increasing since the 1990s and has more than doubled between 1994 and 2001 (Crane 2003). In 2001, there were an estimated 90,232 ED visits related to opioid analgesic abuse, a 117 percent increase since 1994. Nationally, opioid analgesics were involved in 14 percent of all drug-abuse-related ED visits in 2001 (SAMHSA 2002*b*). According to the DAWN Mortality Data Report for 2002 (SAMHSA 2002*c*), hydrocodone ranked among the 10 most common drugs related to deaths in 18 cities, including Detroit (63), Las Vegas (46), Dallas (36), New Orleans (33), and Oklahoma City (31). Oxycodone ranked among the 10 most common drugs related to deaths in 19 cities, including Philadelphia (88), Baltimore (34), Boston (34), Phoenix (34), and Miami (28).

The rise of heroin use appears to be a nationwide phenomenon in the United States.

According to the Office of National Drug Control Policy (ONDCP), there were an estimated 810,000 to 1,000,000 individuals addicted to heroin in the United States in the year 2000—which is the highest number since the mid-to-late 1970s (ONDCP 2003). Several factors have contributed to this increase. Historically, heroin purity has been less than 10 percent. By the late 1990s, however, purity was between 50 and 80 percent. The increase in purity has made heroin easier to use by noninjection routes, such as snorting and smoking. Because individuals can become addicted to or overdose from heroin taken via any route, the increase in the type and number of routes used has led to a rise in new cases of heroin addiction across all sociodemographic categories.

Many addicted individuals may switch to the injection route as their heroin use continues to increase, or if heroin purity should decrease again. An increase in rates of injection drug use would have a significant effect on the incidence of human immunodeficiency virus (HIV) infection, hepatitis B and C, and other infectious diseases.

The rise of heroin use appears to be a nationwide phenomenon in the United States. Heroin overdose deaths have risen sharply, as have ED admissions involving heroin. The most recent data on such ED admissions come from SAMHSA's DAWN reports, which can be accessed via the Web at the following sites: http://dawninfo.samhsa.gov/ or http://www.nida.nih.gov/CEWG/DAWN.html.

Current State of Opioid Addiction Treatment

There are two main modalities for the treatment of opioid addiction: pharmacotherapy and psychosocial therapy. Pharmacotherapies now available for opioid addiction include (1) agonist maintenance with methadone; (2) partial-agonist maintenance with buprenorphine or buprenorphine plus naloxone; (3) antagonist maintenance using naltrexone; and (4) the use of antiwithdrawal ("detoxification") agents (e.g., methadone, buprenorphine, and/or clonidine) for brief periods, and in tapering doses, to facilitate entry into drug-free or antagonist treatment.

Psychosocial approaches (e.g., residential therapeutic communities), mutual-help programs (e.g., Narcotics Anonymous), and 12-Step- or abstinence-based treatment programs are important modalities in the treatment of addiction to heroin and other opioids, either as stand-alone interventions or in combination with pharmacotherapy.

In 2003, more than 200,000 individuals in the United States were maintained on methadone or LAAM (SAMHSA 2002*a*). Although precise data are difficult to obtain, it is estimated that fewer than 5,000 individuals are maintained on naltrexone for opioid addiction. The number of individuals in 12-Step programs is unknown because of the undisclosed nature of the programs and their assurance of anonymity. The number of patients in residential therapeutic community treatment who identify opioids as their primary drugs of abuse is conservatively estimated at 3,000–4,000. (This estimate is derived from various sources, both published, such as Drug Abuse Treatment Outcome Studies [DATOS], and unpublished, such as Therapeutic Communities of America reports, found at http://www.drugabuse.gov/about/organization/despr/DATOS.html and http://www.therapeuticcommunitiesofamerica.org.)

Current Pharmacotherapy Treatment Options for Opioid Addiction

Three traditional types of pharmacotherapy for opioid addiction are described briefly in this section: (1) agonist treatment (e.g., methadone pharmacotherapy), (2) antagonist treatment (e.g., naltrexone), and (3) the use of these and other agents (e.g., clonidine) to help withdrawal from opioid drugs as a means of entry into treatment. A discussion of the new treatment option using buprenorphine follows.

Agonist Pharmacotherapy

Methadone is the most commonly used medication for opioid addiction treatment in the United States. Well-run OTPs—with appropriate drug monitoring, counseling services (individual, group, family), and vocational resources and referrals—have been demonstrated to decrease heroin use and related crime, increase employment, improve physical and mental health (McLellan et al. 1993), and markedly reduce mortality (see the forthcoming TIP *Medication-Assisted Treatment for Opioid Addiction* [CSAT in development[†]]), as well as the incidence of needle sharing (Metzger et al. 1991) and HIV transmission (Metzger et al. 1993). Methadone suppresses opioid withdrawal, blocks the effects of other opioids, and decreases craving for opioids.

Antagonist Pharmacotherapy

Naltrexone is an opioid antagonist that blocks the effects of heroin and most other opioids. It does not have addictive properties or produce physical dependence, and tolerance does not develop. It has a long half-life, and its therapeutic effects can last up to 3 days. Naltrexone is not a stigmatized treatment. It also decreases the likelihood of alcohol relapse when used to treat alcohol dependence.

From a purely pharmacological point of view, naltrexone would appear to have the properties of a useful medication for the treatment of opioid addiction. Its usefulness in the treatment of opioid addiction, however, has been limited because of certain disadvantages. First, many addicted patients are not interested in taking naltrexone because, unlike methadone and LAAM, it has no opioid

[†]Some TIPs are available online at http://www.kap.samhsa.gov/products/manuals/index.htm. Others can be ordered from the National Clearinghouse for Alcohol and Drug Information (NCADI) by accessing its electronic catalog http://store.health.org/catalog/ or by calling 1-800-729-6686. Up to five free hard copies may be ordered using the NCADI order number.

agonist effects; patients continue to experience cravings and are thereby not motivated to maintain adherence to the medication regimen. Second, a patient addicted to opioids must be fully withdrawn for up to 2 weeks from all opioids before beginning naltrexone treatment. Unfortunately, during this withdrawal period, many patients relapse to use of opioids and are unable to start on naltrexone. Furthermore, once patients have started on naltrexone, it may increase the risk for overdose death if relapse does occur.

Naltrexone has demonstrated some utility among subgroups of addicted patients with strong motivation and psychosocial support for treatment and medication adherence (e.g., healthcare professionals, business executives, younger patients, patients involved in the criminal justice system). Because most addicted patients will not voluntarily take naltrexone, however, the number of individuals maintained on it continues to be low. Research is under way on a number of sustained-release, injectable forms of naltrexone in an effort to increase adherence, particularly in the early stages of treatment.

Agents Used To Assist With Withdrawal From Opioid Drugs

Medically supervised withdrawal (detoxification) from opioids is an initial component of certain treatment programs but, by itself, does not constitute treatment of addiction. A variety of agents and methods are available for medically supervised withdrawal from opioids. These include methadone dose-reduction, the use of clonidine and other alpha-adrenergic agonists to suppress withdrawal signs and symptoms, and rapid detoxification procedures (e.g., with a combination of naltrexone or naloxone and clonidine and, more recently, buprenorphine). Each of these methods has strengths and weaknesses. When used properly, various pharmacological agents can produce safe and less uncomfortable opioid withdrawal. As a result of the increasing purity of street heroin, however, physicians are reporting more difficulty managing patients with the use of clonidine and other alpha-adrenergic agonists during withdrawal.

Unfortunately, the majority of individuals addicted to opioids relapse to opioid use after withdrawal, regardless of the withdrawal method used. Too often, physicians and facilities use dose-reduction and withdrawal in isolation without adequate arrangements for the appropriate treatment and support services that decrease the likelihood of relapse and that are usually necessary for long-term recovery. (For more information about agents used to assist with withdrawal, see the forthcoming TIP *Medication-Assisted Treatment for Opioid Addiction* [CSAT in development].)

Buprenorphine: A New Treatment Option for Opioid Addiction

Buprenorphine's pharmacological and safety profile (see chapter 2) makes it an attractive treatment for patients addicted to opioids as well as for the medical professionals treating them. Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa receptor. It has very high affinity and low intrinsic activity at the mu receptor and will displace morphine, methadone, and other opioid full agonists from the receptor. Its partial agonist effects imbue buprenorphine with several clinically desirable pharmacological properties: lower abuse potential, lower level of physical dependence (less withdrawal discomfort), a *ceiling effect* at higher doses, and greater safety in overdose compared with opioid full agonists.

At analgesic doses, buprenorphine is 20–50 times more potent than morphine. Because of its low intrinsic activity at the mu receptor, however, at increasing doses, unlike a full opioid agonist, the agonist effects of buprenorphine reach a maximum and do not continue to increase linearly with increasing doses of

the drug—the ceiling effect. One consequence of the ceiling effect is that an overdose of buprenorphine is less likely to cause fatal respiratory depression than is an overdose of a full mu opioid agonist.

In the pharmacotherapy of opioid addiction, buprenorphine, as a partial opioid agonist, can be thought of as occupying a midpoint between opioid full agonists (e.g., methadone, LAAM) and opioid antagonists (e.g., naltrexone, nalmefene). It has sufficient agonist properties such that individuals addicted to opioids perceive a reinforcing subjective effect from the medication, often described in terms of "feeling normal." In higher doses, and under certain circumstances, its antagonist properties can cause the precipitation of acute withdrawal if administered to an individual who is physically dependent on opioids and maintained on a sufficient dose of a full agonist. In this scenario, buprenorphine can displace the full agonist from the mu receptors, yet not provide the equivalent degree of receptor activation, thereby leading to a net decrease in agonist effect and the onset of withdrawal. (See chapter 2 for more details on such effects.) Furthermore, because of the high affinity of buprenorphine for the opioid receptor, this precipitated abstinence syndrome may be difficult to reverse. Buprenorphine produces a blockade to subsequently administered opioid agonists in a dose-responsive manner. This effect makes the drug particularly appealing to well-motivated patients, as it provides an additional disincentive to continued opioid use.

Buprenorphine can produce euphoria, especially if it is injected. Buprenorphine does produce physical dependence, although it appears to do so to a lesser degree than do full opioid agonists, and it appears to be easier to discontinue at the end of medication treatment.

Buprenorphine has several pharmaceutical uses. It is a potent analgesic, available in many countries as a 0.3–0.4 mg sublingual tablet (Temgesic®). Until 2002, the only form of buprenorphine approved and marketed in the United States was the parenteral form for treatment of pain (Buprenex®). In 2002, two sublingual tablet formulations of buprenorphine were approved by FDA as opioid addiction treatment medications: buprenorphine alone (Subutex®) and a combination tablet containing buprenorphine plus naloxone in a 4:1 ratio (Suboxone®). Both of these tablets are Schedule III opioids and therefore eligible for use in the treatment of opioid addiction under DATA 2000. Figure 1–1 shows the dosage forms of buprenorphine currently available in the United States. Note that, as of the date of this publication, Subutex® and Suboxone® are the only forms of buprenorphine that are indicated and can be legally used for the treatment of opioid addiction in the United States—neither Buprenex® nor its generic equivalent can be used legally to treat opioid addiction.

Many of the large clinical studies of buprenorphine in the treatment of opioid addiction in the United States have been conducted under the joint sponsorship of the National Institute on Drug Abuse (NIDA) and Reckitt Benckiser, the company holding the buprenorphine patent. The most extensive clinical experience with buprenorphine used for treatment of opioid addiction is in France, where the medication has been available for office-based treatment of opioid addiction since February 1996. In France, buprenorphine can be prescribed for

In 2002, two sublingual tablet formulations of buprenorphine were approved by FDA as opioid addiction treatment medications…

Figure 1–1

Dosage Forms of Buprenorphine Available in the United States (as of July 2004)

Medication	Trade Name	Dosage Form(s)	Indication	Company	FDA-Approved for Opioid Addiction Treatment
Buprenorphine	Subutex®	2- or 8-mg sublingual tablets	Opioid addiction	Reckitt Benckiser	Yes
Buprenorphine/ naloxone combination	Suboxone®	2- or 8-mg sublingual tablets with buprenorphine/ naloxone in 4:1 ratio	Opioid addiction	Reckitt Benckiser	Yes
Buprenorphine	Buprenex®	Injectable ampules	Moderate-to-severe pain	Reckitt Benckiser	No
Buprenorphine	Buprenorphine injectable (generic)	Injectable ampules	Moderate-to-severe pain	Abbott Laboratories	No

maintenance treatment by both addiction specialists and general practitioners. It is estimated that close to 70,000 patients are currently receiving maintenance treatment with buprenorphine in France.

Buprenorphine doses studied for opioid addiction treatment have ranged from 1–2 mg to 16–32 mg, depending upon the formulation (solution versus tablet), with duration of treatment lasting from a few weeks to years. Using the outcome measures of illicit opioid use, retention in treatment, and assessment for adverse events, studies have shown that buprenorphine treatment reduces opioid use, retains patients in treatment, has few side effects, and is acceptable to most patients (Johnson 1992; Johnson 2000; Ling 1996; Ling 1998; O'Connor 2000).

Although buprenorphine has been abused and injected by individuals addicted to opioids in countries where the sublingual tablet is available as an analgesic, its abuse potential appears substantially less than that of full opioid agonists. To reduce the potential for abuse even further, the sublingual tablet dosage form combining buprenorphine with naloxone was developed by NIDA and Reckitt Benckiser.

The buprenorphine/naloxone combination tablet appears to have reduced abuse potential compared with buprenorphine alone when studied in opioid-dependent populations. It works on the principle that naloxone is approximately 10–20 times more potent by injection than by the sublingual route. Therefore, if the combination is taken sublingually,

as directed, the small amount of naloxone available should not interfere with the desired effects of buprenorphine. If the combination form is dissolved and injected by an individual physically dependent on opioids, however, the increased bioavailability of naloxone via the parenteral route should precipitate an opioid withdrawal syndrome.

Summary and Overview of the Guidelines

Buprenorphine as a medication, and the circumstances under which it can be used, together provide a new means to treat opioid addiction in the United States. Buprenorphine's usefulness stems from its unique pharmacological and safety profile, which encourages treatment adherence and reduces the possibilities for both abuse and overdose. Because buprenorphine has unusual pharmacological properties, physicians may want to consult with addiction specialists to understand more fully the partial opioid agonist effects of buprenorphine and how these properties are useful in opioid addiction treatment. Although buprenorphine offers special advantages to many patients, it is not for everyone. Care must be taken to assess each patient fully and to develop a realistic treatment plan for each patient accepted for buprenorphine treatment.

Chapter 2 provides additional information on the pharmacological properties of opioids in general and of buprenorphine in particular, along with safety considerations (especially drug interactions). Chapter 3 provides important screening guidelines and specific tools for initially assessing patients. Chapter 4 provides a step-by-step guide for initiating and maintaining treatment and developing a treatment plan. Chapter 5 provides guidelines on the use of buprenorphine with special populations, including, for example, pregnant women, adolescents, individuals leaving controlled environments (e.g., prison), and healthcare professionals who are addicted. Chapter 6 provides important information on policies and procedures relevant to opioid addiction treatment under the DATA 2000 paradigm. References (see appendix A) are provided so that physicians can consult them to develop the best fit for each patient's treatment plan.

As of the date of this publication, Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone) are the only forms of buprenorphine that have received FDA approval for use in opioid addiction treatment. Throughout the remainder of this document, use of the term *buprenorphine* will apply to both sublingual formulations of buprenorphine and to any similarly formulated generic products that may receive FDA approval in the future. When information is presented that is specific to either the buprenorphine monotherapy formulation or to the buprenorphine/naloxone combination, the specific designation will be employed, either by the trade name of the currently approved products (which will be meant to include any similar generic equivalents that may be approved in the future) or by the full formula designation.

The consensus panel notes that these guidelines represent one approach, but not necessarily the only approach, to the treatment of opioid addiction with buprenorphine. The panel considers these guidelines not as inflexible rules that must be applied in every instance, but rather as guidance to be considered in the evaluation and treatment of individual patients. Because each patient is unique, and because scientific knowledge and clinical best practices change over time, the application of these guidelines to the treatment of an individual patient must be informed by the needs of the patient, the changing body of scientific and clinical knowledge, and the clinical judgment of the physician.

2 Pharmacology

In This Chapter...

General Opioid Pharmacology

Pharmacology of Buprenorphine

Buprenorphine Safety, Adverse Reactions, and Drug Interactions

Effectiveness of Buprenorphine Treatment

The Buprenorphine/ Naloxone Combination

Diversion and Misuse of Either Buprenorphine Alone or the Buprenorphine/Naloxone Combination Product

Summary

Overview

Five topics related to the general pharmacology of opioids are reviewed in the first part of this chapter: (1) opioid receptors; (2) functions of opioids at receptors; (3) consequences of repeated administration and withdrawal of opioids; (4) the affinity, intrinsic activity, and dissociation of opioids from receptors; and (5) general characteristics of abused opioids. These topics are followed by a detailed review of the general and applied pharmacology of buprenorphine.

General Opioid Pharmacology

Opioid Receptors

Opioid receptors are molecules on the surfaces of cells to which opioid compounds attach and through which they exert their effects. Different types of opioid receptors are present in the brain. The receptor most relevant to opioid abuse and treatment is the mu receptor. It is through activation of the mu receptor that opioids exert their analgesic, euphorigenic, and addictive effects. The roles of other types of opioid receptors in the brain (that is, non-mu opioid receptors) in the addictive process are not well defined.

The Functions of Opioids at Receptors

Opioids can interact with receptors in different ways. For purposes of this discussion, three types of drug/receptor interactions are described: agonists (or full agonists), antagonists, and partial agonists.

Full Agonists

Drugs that activate receptors in the brain are termed agonists. Agonists bind to receptors and turn them on—they produce an effect

in the organism. Full mu opioid agonists activate mu receptors. Increasing doses of full agonists produce increasing effects until a maximum effect is reached or the receptor is fully activated. Opioids with the greatest abuse potential are full agonists (e.g., morphine, heroin, methadone, oxycodone, hydromorphone).

Antagonists

Antagonists also bind to opioid receptors, but instead of activating receptors, they effectively block them. Antagonists do not activate receptors, and they prevent receptors from being activated by agonist compounds. An antagonist is like a key that fits in a lock but does not open it and prevents another key from being inserted to open the lock. Examples of opioid antagonists are naltrexone and naloxone.

Partial Agonists

Partial agonists possess some of the properties of both antagonists and full agonists. Partial agonists bind to receptors and activate them, but not to the same degree as do full agonists. At lower doses and in individuals who are not dependent on opioids, full agonists and partial agonists produce effects that are indistinguishable. As doses are increased, both full and partial agonists produce increasing effects. At a certain point, however, as illustrated in figure 2–1, the increasing effects of partial agonists reach maximum levels and do not increase further, even if doses continue to rise—the *ceiling effect*. The figure represents any effect mediated by mu opioid receptors (e.g., analgesia, euphoria, respiratory depression). As higher doses are reached, partial agonists can act like antagonists—occupying receptors but not activating them (or only partially activating them), while at the same time displacing or blocking full agonists from receptors. Buprenorphine is an example of a mu opioid partial agonist, and its properties as such are discussed in detail below.

Consequences of Repeated Administration and Withdrawal of Opioid Drugs

The repeated administration of a mu opioid agonist results in tolerance and dose-dependent physical dependence. *Tolerance* is characterized by a decreased subjective and objective response to the same amount of opioids used over time or by the need to keep increasing the amount used to achieve the desired effect. In the case of abuse or addiction, the desired effect typically is euphoria. *Physical dependence* is manifested as a characteristic set of withdrawal signs and symptoms in response to reduction, cessation, or loss of the active compound at receptors (withdrawal syndrome).

Typical signs and symptoms of the *opioid withdrawal syndrome* include lacrimation, diarrhea, rhinorrhea, piloerection, yawning, cramps and aches, pupillary dilation, and sweating. Not all of these signs and symptoms are necessarily present in any single individual experiencing the opioid withdrawal syndrome. Withdrawal, characterized by marked distress, may include drug craving and drug seeking and is frequently associated with relapse to drug use in a patient with opioid addiction. In an individual who otherwise is in good general health (e.g., with no history of significant cardiovascular disease), opioid withdrawal is not life threatening. Patients with cardiovascular disease or other severe conditions will need comanagement involving the appropriate specialist, as well as consultation with an addiction specialist.

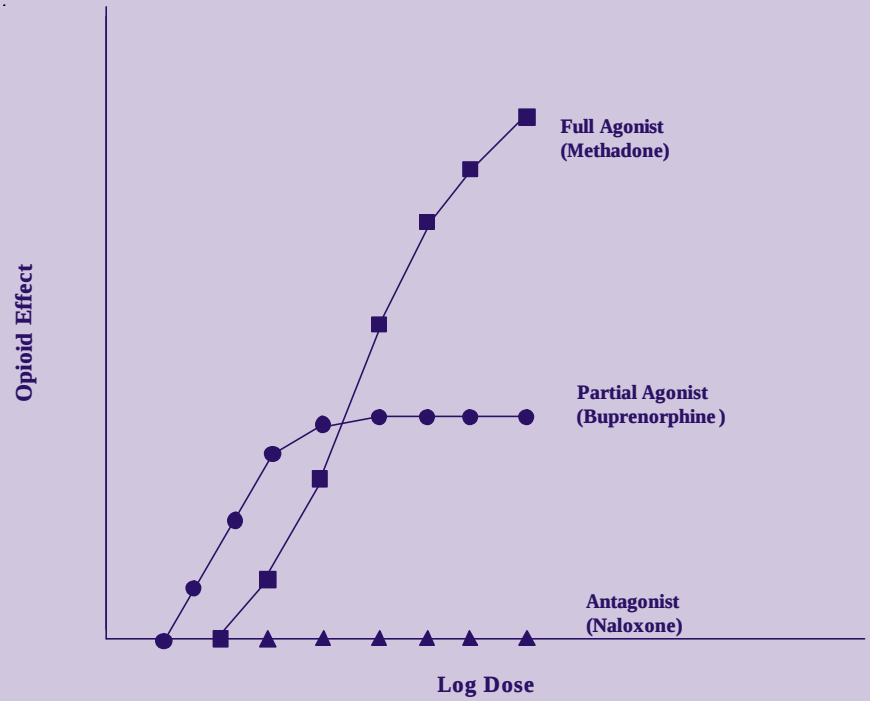
Two types of withdrawal are associated with mu opioid agonists: spontaneous withdrawal and precipitated withdrawal.

Spontaneous Withdrawal

Spontaneous withdrawal can occur when an individual who is physically dependent on mu agonist opioids (e.g., has been using

Figure 2–1

*Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists**



*Conceptual representation only, not to be used for dosing purposes.

opioids on a daily basis) suddenly discontinues that opioid use. It also can occur if an individual who is physically dependent markedly decreases his or her daily opioid use.

In an individual who is physically dependent on heroin, spontaneous withdrawal usually begins 6–12 hours after the last dose and peaks in intensity 36–72 hours after the last use. The spontaneous withdrawal syndrome from heroin lasts approximately 5 days, although a milder, protracted withdrawal may last longer. Other short-acting opioids, such as oxycodone and hydrocodone, have kinetic profiles that are similar to heroin, and the time course of spontaneous withdrawal for these agents should be similar to that documented for heroin. Opioids with longer half-lives have a longer period before the onset of spontaneous withdrawal (e.g., 24–72 hours for methadone) and a longer period before peak withdrawal is experienced.

Precipitated Withdrawal

Precipitated withdrawal also occurs in individuals who are physically dependent on mu agonist opioids. Precipitated withdrawal usually occurs when an individual physically dependent on opioids is administered an opioid antagonist. In an individual who is not physically dependent upon opioids, the acute administration of an antagonist typically produces no effects. In an individual who is physically dependent on opioids, however, an antagonist produces a syndrome of withdrawal

that is qualitatively similar to that seen with spontaneous withdrawal (although the onset is faster and the syndrome is shorter, depending on the half-life of the antagonist). One way to conceptualize precipitated withdrawal is that the antagonist displaces agonists from receptors, but because the antagonist does not activate the receptor, there is a net decrease in agonist effect, resulting in withdrawal.

It is also possible for partial agonists to precipitate withdrawal. If an individual who is physically dependent on opioids receives an acute dose of a partial agonist, the partial agonist can displace the full agonist from the receptors yet not activate the receptors as much as the full agonist had. The net effect would be a decrease in agonist effect and a precipitated withdrawal syndrome. Precipitated withdrawal with a partial agonist is more likely to occur in an individual who has a high level of physical dependence (e.g., high use of opioids each day), who takes the partial agonist soon after a dose of full agonist, and/or who takes a high dose of the partial agonist. These points, discussed in more detail below, are directly relevant to the initiation of buprenorphine treatment.

Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors.

Affinity, Intrinsic Activity, and Dissociation

The strength with which a drug binds to its receptor is termed its *affinity*. The degree to which a drug activates its receptors is termed its *intrinsic activity*. Affinity for a receptor and activation of the receptor are two different qualities of a drug. A drug can have high affinity for a receptor but not activate the receptor (e.g., an antagonist). Mu opioid agonists, partial agonists, and antagonists can vary in their affinity.

In addition to variations in affinity and intrinsic activity, drugs also vary in their rate of *dissociation* from receptors. Dissociation is a measure of the disengagement or uncoupling of the drug from the receptor. Dissociation is not the same as affinity—a drug can have high affinity for a receptor (it is difficult to displace it from the receptor with another drug once the first drug is present), but it still dissociates or uncouples from the receptor with some regularity. Buprenorphine's slow dissociation contributes to its long duration of action.

Characteristics of Abused Drugs

The rate of onset of the pharmacological effects of a drug, and thereby its abuse potential, is determined by a number of factors. Important among these are the drug's route of administration, its half-life, and its lipophilicity (which determines how fast the drug reaches the brain). A faster route of drug administration (e.g., injection, smoking), a shorter half-life, and a faster onset of action all are associated with a higher abuse potential of a drug. With all classes of drugs of abuse, it has been shown that the likelihood of abuse is related to the ease of administration, the cost of the drug, and how fast the user experiences the desired results after the drug's administration. In this respect, heroin is highly abusable, as it currently is inexpensive; can be snorted, smoked, or injected; and produces a rapid euphorigenic response.

Pharmacology of Buprenorphine

Overview

Buprenorphine is a thebaine derivative that is legally classified as a narcotic. It is available in numerous countries for use as an analgesic. When used as an analgesic, buprenorphine is

usually given by injection, via a sublingual tablet, or as a transdermal patch, and doses are relatively low (compared with doses used in the treatment of opioid addiction). The typical analgesic dose of buprenorphine is 0.3–0.6 mg (intramuscular or intravenous), and its analgesic effects last about 6 hours.

Buprenorphine is a partial agonist that exerts significant actions at the mu opioid receptor. As reviewed in the previous section, however, its maximal opioid effects are less than that of full agonists, and reach a *ceiling* where higher doses do not result in increasing effect. Because it is a partial agonist, higher doses of buprenorphine can be given with fewer adverse effects (e.g., respiratory depression) than are seen with higher doses of full agonist opioids. Past a certain point, dose increases of buprenorphine do not further increase the pharmacological effects of the drug but do increase its duration of withdrawal suppression and opioid blockade.

At low doses, buprenorphine is many times more potent than morphine. Individuals who are not dependent on opioids but who are familiar with the effects of opioids experience a subjectively positive opioid effect when they receive an acute dose of buprenorphine. These subjective effects aid in maintaining compliance with buprenorphine dosing in patients who are addicted to opioids.

Affinity, Intrinsic Activity, and Dissociation

Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors. Buprenorphine displaces morphine, methadone, and other full opioid agonists from receptors. It also can block the effects of other opioids (Bickel et al. 1988; Rosen et al. 1994; Strain et al. 2002). Because of buprenorphine's higher affinity for the mu receptor, full agonists cannot displace it and therefore will not exert an opioid effect on receptors already occupied by buprenorphine. This effect is dose related, as shown by Comer et al. (2001) in a study demonstrating that the 16-mg dose of the sublingual buprenorphine-alone tablet was more effective than the 8-mg dose in blocking the reinforcing effects of heroin. Similarly, it is difficult for opioid antagonists (e.g., naloxone) to displace buprenorphine and precipitate withdrawal.

Buprenorphine has a slow dissociation rate from the mu opioid receptor, which gives rise to its prolonged suppression of opioid withdrawal and blockade of exogenous opioids. This enables buprenorphine dosing to occur on a less frequent basis than full opioid agonists (Amass et al. 1994*a*,*b*, 1998, 2000, 2001). Buprenorphine can be given as infrequently as three times per week (Amass et al. 2001; Perez de los Cobos et al. 2000; and Schottenfeld et al. 2000). Buprenorphine's effectiveness as a medication for the treatment of opioid addiction on a daily or less-than-daily basis contrasts with its relatively short duration of action as an analgesic.

Bioavailability

Buprenorphine has poor gastrointestinal (GI) bioavailability (Brewster et al. 1981; Walter and Inturrisi 1995), and fair sublingual bioavailability. (See figure 2–2.) FDA-approved formulations of the drug for treatment of opioid addiction are in the form of sublingual tablets that are held under the tongue and absorbed through the sublingual mucosa. Studies of sublingually administered buprenorphine have employed either an alcohol-based solution or a tablet formulation of the drug. Confusion may result when reviewing the literature on the effectiveness of buprenorphine at various doses because most early trials and clinical studies of buprenorphine were performed with a sublingually administered liquid preparation, whereas the oral formulations marketed in the United States are sublingual tablets. Studies have shown that the bioavailability of buprenorphine in sublingual tablet form is significantly less than via sublingual liquid solution—about 50–70 percent that of the liquid form (Nath et al. 1999; Schuh and Johanson 1999), so the dosages of buprenorphine sublingual tablets

Figure 2–2

Bioavailability of Buprenorphine

Route of Administration	Buprenorphine Bioavailability Relative to Intravenous Route of Administration	Buprenorphine Bioavailability Relative to Intramuscular Route of Administration	Buprenorphine Bioavailability Relative to Sublingual Solution Route of Administration
Intravenous	100%	—	—
Intramuscular	70%	100%	—
Sublingual Solution	49%	70%	100%
Sublingual Tablet	29%	42%	50–70%

Sources: Brewster et al. 1981; Kuhlman et al. 1996; Lloyd-Jones et al. 1980; Nath 1999; Schuh and Johanson 1999; Strain and Stitzer 1999; Weinberg et al. 1988

must be significantly higher than those used in the liquid form to achieve the same therapeutic effect.

Abuse Potential

Epidemiological studies and human laboratory studies indicate that buprenorphine is abusable. This is consistent with its action at the mu opioid receptor. The abuse potential, however, is lower in comparison with the abuse potential of full opioid agonists. This is consistent with buprenorphine's partial agonist effects and the resultant ceiling in maximal effects produced. Still, abuse of the analgesic form of buprenorphine through diversion to the injectable route has been reported internationally:

- England (Strang 1985)
- Ireland (O'Connor et al. 1988)
- Scotland (Gray et al. 1989; Morrison 1989; Sakol et al. 1989)
- India (Chowdhury and Chowdhury 1990; Singh et al. 1992)
- New Zealand (Robinson et al. 1993)

Abuse of buprenorphine has been reported to occur via the sublingual and intranasal routes but primarily via diversion of sublingual tablets to the injection route. In a study from France (Obadia et al. 2001), sublingual, buprenorphine-only tablets (Subutex®), marketed for the treatment of opioid addiction, were diverted to the injection route.

Laboratory studies with inpatient subjects have examined the effects of buprenorphine relevant to abuse potential in two populations: (1) subjects who have a history of opioid abuse but are not physically dependent on opioids, and (2) subjects who are physically dependent on opioids.

Abuse Potential in Nonphysically Dependent Opioid Users

In nonphysically dependent opioid users, acute parenteral doses of buprenorphine produce typical mu agonist opioid effects (e.g., pupillary constriction, mild euphoria), suggesting that this population could abuse

buprenorphine (Jasinski et al. 1978, 1989; Pickworth et al. 1993). Similar effects can occur in this population when buprenorphine is administered via other routes, including the sublingual route (Jasinski et al. 1989; Johnson et al. 1989; Walsh et al. 1994). Strain et al. (2000) recently reconfirmed the opioid-like effects of sublingually administered buprenorphine in this population. These researchers further found that, in nondependent subjects, the addition of naloxone (in the buprenorphine/naloxone combination tablet) did not attentuate buprenorphine's opioid effects via the sublingual route. The onset of effects via the sublingual route is slower than that seen with parenteral administration, suggesting that the abuse potential by this route is lower than via the parenteral route.

Abuse Potential in Physically Dependent Opioid Users

The abuse potential of buprenorphine in individuals who are physically dependent on opioids varies as a function of three factors: (1) level of physical dependence, (2) time interval between administration of the full agonist and of buprenorphine, and (3) the dose of buprenorphine administered.

Level of Physical Dependence. In individuals with a high level of physical dependence (e.g., those using substantial amounts of opioids on a daily basis), buprenorphine may precipitate withdrawal when taken during the time of opioid intoxication or receptor occupancy. The relationship between level of physical dependence and buprenorphine-related precipitated withdrawal has been investigated primarily in subjects maintained on methadone. For example, patients maintained on 60 mg of methadone daily can experience precipitated withdrawal from acute doses of sublingual buprenorphine (Walsh et al. 1995). Conversely, in individuals with a low level of physical dependence (e.g., patients maintained on <30 mg per day of methadone), buprenorphine could produce opioid agonist effects, thus suggesting a potential for abuse.

Time Interval. The abuse potential of buprenorphine in opioid-dependent individuals also varies as a function of the time interval between the dose of agonist and the dose of buprenorphine. At relatively short time intervals (e.g., 2 hours after a dose of methadone), buprenorphine can precipitate withdrawal—even when the level of physical dependence is relatively low (Strain et al. 1995). At longer time intervals, it becomes more likely that buprenorphine will exhibit either no effects (i.e., similar to placebo [Strain et al. 1992]) or effects similar to opioid agonists.

Acute Dose of Buprenorphine. Finally, the dose of buprenorphine administered also can influence its abuse potential. Low doses of injected buprenorphine (e.g., ≤2 mg) produce minimal effects in opioid-dependent patients and are primarily identified as similar to placebo (Strain et al. 1992) although there has been at least one report of more precipitated abstinence (Banys et al. 1994).

Higher doses can be identified as opioid agonist-like, especially as the time interval since the dose of agonist increases (e.g., 24 or more hours) and if the individual has a lower level of physical dependence (e.g., 30 mg per day of methadone or the equivalent).

Although buprenorphine can precipitate withdrawal under certain circumstances, it is worth noting that it does not usually produce severe precipitated withdrawal symptoms.

Potential for Physical Dependence

Repeated administration of buprenorphine produces or maintains opioid physical dependence; however, because buprenorphine is a partial agonist, the level of physical dependence appears to be less than that produced by full agonists (Eissenberg et al. 1996). Furthermore, the withdrawal syndrome associated with buprenorphine discontinuation may be significantly milder in intensity, and the onset of withdrawal signs

and symptoms slower, than that seen with full mu agonists (Eissenberg et al. 1997; Jasinski et al. 1978; Mello et al. 1982; San et al. 1992). The reason for the slower onset of withdrawal symptoms is not completely understood but is likely related to buprenorphine's slow dissociation from the mu receptor. Gradual dose reduction of buprenorphine results in an even milder withdrawal syndrome.

Metabolism and Excretion

A high percentage of buprenorphine is bound to plasma protein and is metabolized in the liver by the cytochrome P450 3A4 enzyme system into norbuprenorphine and other products (Iribarne et al. 1997; Kobayashi et al. 1998). First-pass effects account for its relatively low GI bioavailability and its short plasma half-life. (See the buprenorphine package inserts for a more detailed explanation of its metabolism and excretion.)

Side Effects

The primary side effects of buprenorphine are similar to other mu opioid agonists (e.g., nausea, vomiting, constipation), but the intensity of these side effects may be less than that produced by full agonist opioids.

Buprenorphine Safety, Adverse Reactions, and Drug Interactions

Accidental Ingestion and Overdose

Because of buprenorphine's poor GI bioavailability, swallowing the tablets will result in a milder effect compared with administering them sublingually. (By extrapolation, buprenorphine tablets are approximately one-fifth as potent when swallowed versus when taken sublingually.) Buprenorphine's ceiling effect also adds to its safety in accidental or intentional overdose.

Preclinical studies suggest that high acute doses of buprenorphine (analogous to an overdose) produce no significant respiratory depression or other life-threatening sequelae (e.g., circulatory collapse). Overdose of buprenorphine combined with other medications, however, may increase morbidity and mortality, as described further below.

Respiratory Depression

In contrast to full mu agonists, overdose of buprenorphine (by itself) does not appear to cause lethal respiratory depression in non-compromised individuals. Consistent with this clinical observation, a preclinical study of buprenorphine showed initial dose-related increases in pCO_2 (arterial carbon dioxide level) followed by decreases in pCO_2 compatible with buprenorphine's bell-shaped dose-response curve (Cowan et al. 1977). However, although none of the outpatient clinical trials comparing buprenorphine to methadone or placebo reported adverse events of respiratory depression, some cases have been reported of respiratory depression induced by buprenorphine in individuals not physically dependent on opioids (Gal 1989; Thörn et al. 1988). In addition, buprenorphine, in combination with other sedative drugs, has been reported to produce respiratory depression. (See "Drug Interactions" below.)

Cognitive and Psychomotor Effects

Available evidence in patients maintained on buprenorphine indicates no clinically significant disruption in cognitive and psychomotor performance (Walsh et al. 1994).

Hepatic Effects

Elevation in liver enzymes (AST and ALT) has been reported in individuals receiving buprenorphine (Lange et al. 1990; Petry et al. 2000). There also appears to be a possible

association between intravenous buprenorphine misuse and liver toxicity (Berson et al. 2001). See Johnson et al. 2003*b* for further details. Mild elevations in liver enzymes have been noted in patients with hepatitis who received long-term buprenorphine dosing (Petry 2000).

Perinatal Effects

There is limited clinical experience with buprenorphine maintenance in pregnant women who are addicted to opioids. The literature in this area is limited to case reports, prospective studies, and open-labeled controlled studies; however, no randomized controlled studies have been reported (Johnson et al. 2003*b*). See "Pregnant Women and Neonates" in chapter 5 for a detailed discussion of the available clinical and research evidence.

Buprenorphine-Induced Precipitated Withdrawal

Administration of buprenorphine can precipitate an opioid withdrawal syndrome. Although there is much variability in response to buprenorphine, precipitated withdrawal symptoms tend to be milder than those produced by antagonist-precipitated withdrawal, and intervention is rarely required. In controlled studies in which buprenorphine was given to individuals who were physically dependent on opioids, the precipitated withdrawal syndrome was both mild in intensity and easily tolerated (Strain et al. 1995). However, at least one open-label small-sample trial of low-dose buprenorphine caused a patient to experience pronounced, precipitated, and poorly tolerated withdrawal of severe intensity (Banys et al. 1994). The probability of precipitating a withdrawal syndrome is minimized by reducing the dose of mu agonist before buprenorphine treatment is initiated, by allowing a longer elapsed interval between last agonist dose and first buprenorphine dose, and by starting treatment with a lower buprenorphine dose.

Drug Interactions

Benzodiazepines and Other Sedative Drugs

There have been case reports of deaths apparently associated with injections of buprenorphine combined with benzodiazepines and/or other central nervous system (CNS) depressants (e.g., alcohol) (Reynaud et al. 1998*a*,*b*). Gaulier et al. (2000) reported a case of fatal overdose in which buprenorphine and its metabolites, as well as the metabolites of flunitrazepam, were very high at the time of death. Although it is not known if this is a pharmacodynamic interaction, Ibrahim et al. (2000) and Kilicarslan and Sellers (2000) suggest that, because of buprenorphine's weak ability to inhibit the cytochrome P450 3A4 system, the effect is more likely pharmacodynamic. This interaction, however, underscores the importance for physicians to be cautious in prescribing buprenorphine in conjunction with benzodiazepines, as well as in prescribing buprenorphine to patients who are addicted to opioids and also are abusing or are addicted to benzodiazepines. It is prudent to assume that these cautions also should be applied to buprenorphine combined with other CNS depressants, including alcohol and barbiturates.

> …overdose of buprenorphine (by itself) does not appear to cause lethal respiratory depression in noncompromised individuals.

Opioid Antagonists

Buprenorphine treatment should not be combined with opioid antagonists (e.g.,

naltrexone). It is common for individuals who are addicted to opioids to be concurrently dependent on alcohol. Although naltrexone may decrease the likelihood of relapse to drinking, patients maintained on opioids should not be given naltrexone to prevent alcohol relapse since the naltrexone can precipitate an opioid withdrawal syndrome in buprenorphine-maintained patients. Thus, physicians should not prescribe naltrexone for patients being treated with buprenorphine for opioid addiction.

Medications Metabolized by Cytochrome P450 3A4

Buprenorphine is metabolized by the cytochrome P450 3A4 enzyme system. Other medications that interact with this enzyme system should be used with caution in patients taking buprenorphine. No controlled studies, however, have examined these pharmacokinetic interactions. Figure 2–3 lists some of the drugs known to be metabolized by cytochrome P450 3A4. In some cases, these drugs may either enhance or decrease buprenorphine's effects through actions on the cytochrome P450 3A4 system.*

Opioid Agonists

Clinical situations may arise in which a full agonist may be required for patients who currently are being treated with buprenorphine, such as in the treatment of acute pain. Although this medication interaction has not been studied systematically, the pharmacological characteristics of buprenorphine suggest that it may be difficult to obtain adequate analgesia with full agonists in patients stabilized on maintenance buprenorphine.

Data nonspecific to buprenorphine suggest that, in patients maintained chronically on methadone, the acute administration of full mu agonists for analgesia can be effective. If the necessity should arise for the use of a full mu agonist for pain relief in a patient maintained on buprenorphine, the buprenorphine should be discontinued until the pain can be controlled without the use of opioid pain medications. It must be recognized that treatment with full mu agonists for pain relief will produce increased opioid tolerance and a higher degree of physical dependence. See "Patients With Pain" in chapter 5 for a detailed discussion of the treatment of pain in patients maintained on buprenorphine.

Effectiveness of Buprenorphine Treatment

Buprenorphine can be used for either long-term maintenance or for medically supervised withdrawal (detoxification) from opioids. The preponderance of research evidence and clinical experience, however, indicates that opioid maintenance treatments have a much higher likelihood of long-term success than do any forms of withdrawal treatment. In any event, the immediate goals in starting buprenorphine should be stabilization of the patient and abstinence from illicit opioids, rather than any arbitrary or predetermined schedule of withdrawal from the prescribed medication.

Maintenance Treatment

A number of clinical trials have established the effectiveness of buprenorphine for the maintenance treatment of opioid addiction. These have included studies that compared buprenorphine to placebo (Johnson et al. 1995; Ling et al. 1998; Fudala et al. 2003), as well as comparisons to methadone (e.g., Johnson et al. 1992; Ling et al. 1996; Pani et al. 2000; Petitjean et al. 2001; Schottenfeld et al. 1997; Strain et al. 1994*a*, 1994*b*) and to

*It is important to understand that in vitro findings may not be predictive of what occurs in humans, underscoring the need for clinicians to monitor patients for potential drug interactions and associated adverse events.

Figure 2–3

Partial List of Medications Metabolized by Cytochrome P450 3A4

Inhibitors (potentially increasing blood levels of buprenorphine)	Substrates		Inducers (potentially decreasing blood levels of buprenorphine)
Amiodarone	Alprazolam	Loratadine	Carbamazepine
Clarithromycin	Amlodipine	Losartan	Dexamethasone
Delavirdine	Astemizole	Lovastatin	Efavirenz
Erythromycin	Atorvastatin	Miconazole	Ethosuximide
Fluconazole	Carbamazepine	Midazolam	Nevirapine
Fluoxetine	Cisapride	Navelbine	Phenobarbital
Fluvoxamine	Clindamycin	Nefazadone	Phenytoin
Grapefruit Juice	Clonazepam	Nelfinavir	Primadone
Indinavir	Cyclobenzaprine	Nicardipine	Rifampin
Itraconazole	Cyclosporine	Nifedipine	
Ketoconazole	Dapsone	Nimodipine	
Metronidazole	Delavirdine	Ondansetron	
Miconazole	Dexamethasone	Oral Contraceptives	
Nefazadone	Diazepam	Paclitaxel	
Nelfinavir	Diltiazem	Prednisone	
Nicardipine	Disopyramide	Progestins	
Norfloxacin	Doxorubicin	Quinidine	
Omeprozol	Erythromycin	Rifampin	
Paroxetine	Estrogens	Ritonavir	
Ritonavir	Etoposide	R-Warfarin	
Saquinavir	Felodipine	Saquinavir	
Sertraline	Fentanyl	Sertraline	
Verapamil	Fexofenadine	Simvastatin	
Zafirlukast	Glyburide	Tacrolimus	
Zileuton	Ifosfamide	Tamoxifen	
	Indinavir	Verapamil	
	Ketoconazole	Vinblastine	
	Lansoprazole	Zileuton	
	Lidocaine		

For a continuously updated list of cytochrome P450 3A4 drug interactions, visit http://medicine.iupui.edu/flockhart/table.htm.

methadone and levo-alpha-acetyl-methadol (LAAM) (Johnson et al. 2000). Results from these studies suggest that buprenorphine in a dose range of 8–16 mg a day sublingually is as clinically effective as approximately 60 mg a day of oral methadone, although it is unlikely to be as effective as full therapeutic doses of methadone (e.g., 120 mg per day) in patients requiring higher levels of full agonist activity for effective treatment.

A meta-analysis comparing buprenorphine to methadone (Barnett et al. 2001) concluded that buprenorphine was more effective than 20–35 mg of methadone but did not have as robust an effect as 50–80 mg methadone—much the same effects as the individual studies have concluded.

Buprenorphine's partial mu agonist properties make it mildly reinforcing, thus

encouraging patient compliance with regular administration. This is in contrast to medications such as naltrexone, which also blocks the effects of opioid agonists but lacks any agonist effects. Because a medication such as naltrexone is not reinforcing, adherence in therapeutic use is poor. Naltrexone also may increase the risk for overdose death in the event of relapse following its discontinuation.

Medically Supervised Withdrawal

Although controlled clinical studies of the use of buprenorphine as an agent for treating opioid withdrawal (detoxification) are scarce, some clinical research on its use for this indication has been conducted (Parran et al. 1994). In general, buprenorphine has been used in three ways for withdrawal from opioids: long-period withdrawal (>30 days), usually on an outpatient basis; moderate-period withdrawal (>3 days but <30 days), again on an outpatient basis; and short-period withdrawal (<3 days), which often has been conducted on an inpatient basis. The available evidence from buprenorphine and methadone research suggests that long-period buprenorphine withdrawal probably would be more effective than moderate- or short-period withdrawals but that all forms of withdrawal are less effective compared with ongoing opioid maintenance (Amass et al. 1994*a*,*b*; Sees et al. 2000).

> The safety and efficacy profile of sublingual buprenorphine/naloxone appears to be equivalent to that of buprenorphine alone….

Long-Period Withdrawal. Although few data are available on the use of buprenorphine for gradual withdrawal over a period of months, the literature on opioid withdrawal can be used to guide recommendations in this regard. This literature suggests that using buprenorphine for gradual detoxification is more effective than its use for rapid detoxification in terms of patient compliance and relapse to opioid use. These findings are analogous to those seen with methadone which show that patients undergoing a 10-week methadone dose reduction (i.e., 10 percent per week) had a higher rate of opioid-positive urine samples than those receiving a 30-week dose reduction (i.e., 3 percent per week) and asked for more schedule interruptions (Senay et al. 1977).

Moderate-Period Withdrawal. Few studies of withdrawal from illicit opioids have been conducted using buprenorphine for moderate periods (>3 days, but <30 days). Moderate-period withdrawal using buprenorphine suppresses signs and symptoms of withdrawal, is tolerated by patients, and is safe. For example, a study comparing 10 days of buprenorphine versus clonidine for the inpatient treatment of opioid withdrawal found buprenorphine superior to clonidine in relieving withdrawal signs and symptoms (Nigam et al. 1993). Outcomes with moderate-period withdrawal, however, are unlikely to be as positive as those seen with long-period withdrawal (Amass et al. 1994*a*,*b*).

Short-Period Withdrawal. The liquid form of buprenorphine has been studied for the withdrawal from opioids over short periods (e.g., 3 days) (Armenian et al. 1999). In these studies, the doses of buprenorphine administered were low (compared to maintenance doses) and typically were administered two or three times per day, either by injection or by having the patient hold the liquid under his or her tongue. (Note that this off-label use of the liquid form of buprenorphine is unlawful outside an approved study setting and is now unnecessary due to the FDA approval of Subutex® and Suboxone®.)

Reports have indicated that buprenorphine is well accepted by patients for short-period withdrawal and that opioid withdrawal signs and symptoms are suppressed (DiPaula et al.

2002; and Bickel et al. 1988). When compared with clonidine for the treatment of short-period withdrawal, buprenorphine is better accepted by patients and more effective in relieving withdrawal symptoms (Cheskin et al. 1994). Long-term outcomes from short-period opioid withdrawal using buprenorphine have not been reported, however, and studies of other withdrawal modalities have shown that brief withdrawal periods do not produce measurable long-term benefits (Simpson and Sells 1989); patients usually relapse to opioid use.

The Buprenorphine/ Naloxone Combination

There have been reports from several countries of abuse of buprenorphine by injection. Because of this buprenorphine abuse, a sublingual tablet form containing naloxone has been developed for the U.S. market to decrease the potential for abuse of the combination product via the injection route. Sublingual naloxone has relatively low bioavailability (Preston et al. 1990), while sublingual buprenorphine has good bioavailability. (Both naloxone and buprenorphine have poor GI bioavailability.) Thus, if a tablet containing buprenorphine plus naloxone is taken as directed—sublingually—the patient will experience a predominant buprenorphine effect. However, if an opioid-dependent individual dissolves and injects the combination tablet, then the antagonistic effect of naloxone predominates because of its high parenteral bioavailability (Stoller et al. 2001). Under such circumstances, the individual should experience a precipitated withdrawal syndrome. This should decrease the likelihood of misuse and abuse of the combination tablet by the injection route.

The safety and efficacy profile of sublingual buprenorphine/naloxone appears to be equivalent to that of buprenorphine alone (Harris et al. 2000). Currently, no special safety or side-effect considerations exist for the combination formulation, but it is not recommended for use in pregnant women. If buprenorphine treatment is elected for a pregnant woman, the monotherapy product should be used. (See "Pregnant Women and Neonates" in chapter 5.)

Diversion and Misuse of Either Buprenorphine Alone or the Buprenorphine/ Naloxone Combination Product

As with any prescription opioid, physicians prescribing or dispensing buprenorphine or the buprenorphine/naloxone combination should monitor patients for diversion of these medications. As noted above, naloxone is combined with buprenorphine to decrease the potential for abuse of the combination via injection. Four types of individuals might attempt to abuse buprenorphine or buprenorphine/naloxone tablets parenterally:

1. *Those using diverted tablets who are physically dependent on illicit opioids (e.g., heroin).* Parenteral use of the combination buprenorphine/naloxone tablet by these individuals would result in precipitated withdrawal more reliably than injection of buprenorphine alone.
2. *Those using diverted tablets who are taking therapeutic full agonist opioids (e.g., oxycodone, methadone).* Parenteral use of the combination buprenorphine/naloxone tablet by these individuals also would result in a precipitated withdrawal syndrome more reliably than injection of buprenorphine alone.
3. *Those receiving prescription buprenorphine or buprenorphine/naloxone tablets who dissolve and inject their own medication.* This population would experience an agonist effect from buprenorphine but no antagonist effect from naloxone, as large doses of opioid antagonists are needed to precipitate withdrawal in buprenorphine-maintained subjects

(Eissenberg et al. 1996). Although some of the agonist effects of buprenorphine may be attenuated by the simultaneous injection of naloxone, acute agonist effects will still be experienced whether the combination or the monotherapy product is injected.

4. *Those who abuse opioids but who are not physically dependent on them*. In this group, neither naloxone nor buprenorphine will produce precipitated withdrawal. Sublingual or injected use of either buprenorphine product will produce opioid agonist effects; however, the euphoric effects would be mild.

Summary

An understanding of both the general pharmacology of opioids and the specific pharmacological properties of buprenorphine is essential for physicians who intend to treat opioid addiction with buprenorphine. Buprenorphine has unique qualities that make it an effective and safe addition to the available pharmacological treatments for opioid addiction. The combination of buprenorphine with the opioid antagonist naloxone further increases its safety and decreases—but does not eliminate—the likelihood of diversion and misuse.

3 Patient Assessment

In This Chapter...

Screening and Assessment of Opioid Use Disorders

Determining Appropriateness for Buprenorphine Treatment

Overview

This chapter presents guidance on screening for the presence of opioid use disorders and for the further assessment of patients in whom screening indicates the potential presence of a problem. Guidelines are provided for determining when buprenorphine is an appropriate treatment option for patients who have an opioid addiction. Additional information about many of the topics discussed in this chapter can be found in appendix E.

Screening and Assessment of Opioid Use Disorders

Screening

The consensus panel that developed the *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* recommends that physicians periodically and regularly screen *all* patients for substance use and substance-related problems, not just those patients who fit the stereotypical picture of addiction. Although addiction to drugs and alcohol is common, currently fewer than one-third of physicians in the United States carefully screen for addiction (National Center on Addiction and Substance Abuse 2000).

Conducting ongoing, regular substance abuse screening as part of medical care facilitates the early identification, intervention, and treatment of addiction. Periodic assessments for abuse, addiction, or other adverse effects are particularly helpful when the primary care physician or specialist is prescribing opioids for the treatment of pain. Office-based physicians may conduct further assessment and provide primary opioid addiction treatment for those patients who are determined to be appropriate candidates for office-based treatment. Alternatively, when indicated, patients may be referred for treatment in another setting.

Goals of Screening

The goals of addiction screening and assessment are to

- Identify individuals who are at risk for developing drug- or alcohol-related problems
- Identify individuals who may have developed drug- or alcohol-related problems or addiction
- Identify individuals who require further medical or addiction assessment
- Diagnose addiction or other substance-related disorders
- Develop recommendations and plan for appropriate addiction treatment
- Assess the biopsychosocial needs of patients with addictions

Initial Screening

Initial screening should consist of a combination of objective screening instruments, laboratory evaluations, and interview(s). If the physician suspects an addiction problem after reviewing the initial results, further assessment is indicated. In-depth interviews and standardized assessments are the most effective means of gathering further information.

To determine the appropriateness of office-based or other opioid agonist treatment, a comprehensive patient assessment is essential.

Several validated addiction screening instruments are available. In addition, many physicians develop their own set of screening questions for medical illnesses. Screening questionnaires may be given to all patients in a physician's practice, not just to those patients considered to be "at risk" for drug or alcohol problems.

Examples of addiction screening instruments include

- Drugs:
  - COWS (Clinical Opiate Withdrawal Scale) (Wesson et al. 1999)
  - SOWS (Subjective Opiate Withdrawal Scale) (Bradley et al. 1987; Gossop 1990; Handelsman et al. 1987)
  - DAST-10 (Drug Abuse Screening Test) (Skinner 1982)
  - CINA (Clinical Institute Narcotic Assessment Scale for Withdrawal Symptoms) (Peachey and Lei 1988)
  - CAGE-AID (CAGE Adapted to Include Drugs) (Brown and Rounds 1995)
  - Narcotic Withdrawal Scale (Fultz and Senay 1975)
- Alcohol:
  - CAGE (Maisto et al. 2003)
  - AUDIT (Alcohol Use Disorders Identification Test) (Babor et al. 2001)
  - MAST (Michigan Alcohol Screening Test) (Selzer 1971)
  - SMAST (Short Michigan Alcohol Screening Test) (Selzer et al. 1975)

For more information about such tools, see appendix B. The reader also can review the Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Treatment (CSAT) TIP 24, *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT 1997). See http://www.kap.samhsa.gov/products/manuals/index.htm.

Assessment

If screening indicates the presence of an opioid use disorder, further assessment is indicated to thoroughly delineate the patient's problem, to identify comorbid or complicating medical or emotional conditions, and to determine the appropriate treatment setting and level of treatment intensity for the patient. To determine the appropriateness of office-based or other opioid agonist treatment, a comprehensive

patient assessment is essential. The assessment may be accomplished in stages over a 3- to 4-week period, during initiation of treatment and gradual acquisition of increasingly detailed information. Several office visits may be required to obtain all the information necessary to make a comprehensive set of diagnoses and to develop an appropriate treatment plan, although these efforts also can be completed in a single, extended visit if so desired. Treatment should not be delayed, however, pending complete patient assessment.

Goals of Assessment

The goals of the medical assessment of a patient who is addicted to opioids are to

- Establish the diagnosis or diagnoses
- Determine appropriateness for treatment
- Make initial treatment recommendations
- Formulate an initial treatment plan
- Plan for engagement in psychosocial treatment
- Ensure that there are no contraindications to the recommended treatments
- Assess other medical problems or conditions that need to be addressed during early treatment
- Assess other psychiatric or psychosocial problems that need to be addressed during early treatment

Components of Assessment

The components of the assessment of a patient who is addicted to opioids should include

- Complete history
- Physical examination
- Mental status examination
- Relevant laboratory testing
- Formal psychiatric assessment (if indicated)

In forming a framework for assessment, physicians may include questions and evaluations pertinent to the most recent edition of the American Society of Addiction Medicine Patient Placement Criteria (ASAM PPC) and the categories of the Addiction Severity Index (ASI) (Mee-Lee 2001; McLellan et al. 1992). The ASAM PPC may be ordered from ASAM at http://www.asam.org. The full text of the ASI can be downloaded from the Treatment Research Institute Web site at http://www.tresearch.org.

Complete History Taking—Interviewing Patients Who Are Addicted

Attitude of the Physician. The approach and attitude the physician shows to patients who have an addiction are of paramount importance. Patients are often hesitant or reluctant to disclose their drug use or problems. Patients who are addicted report discomfort, shame, fear, distrust, hopelessness, and the desire to continue using drugs as reasons they do not discuss addiction openly with their physicians (National Center on Addiction and Substance Abuse 2000). Patients in treatment for pain may fear the loss of their opioid pain medications should they disclose to a physician their concerns about their possible addiction. Physicians need to approach patients who have an addiction in an honest, respectful, matter-of-fact way, just as they would approach patients with any other medical illness or problem. A physician's responsibility is to deal appropriately with his or her own attitudes and emotional reactions to a patient. For evaluation to be effective, personal biases and opinions about drug use, individuals who have addictions, sexual behavior, lifestyle differences, and other emotionally laden issues must be set aside or dealt with openly and therapeutically.

Certain characteristics of treatment providers facilitate effective evaluation and treatment of addiction, and these characteristics should be cultivated by physicians who plan to treat patients who have addictions (CSAT 1999*b*; Miller et al. 1993; Najavits and Weiss 1994). These attributes are listed in figure 3–1.

Figure 3–1

Attributes of an Effective Addiction Treatment Provider

- Ability to establish a helping alliance
- Good interpersonal skills
- Nonpossessive warmth
- Friendliness
- Genuineness
- Respect
- Affirmation
- Empathy
- Supportive style
- Patient-centered approach
- Reflective listening

Targeted, open-ended questions, such as those presented in figure 3–2, about the use of drugs and alcohol will elicit more information than simple, closed-ended, "yes" or "no" or single-answer questions. Refer to TIP 34, *Brief Interventions and Brief Therapies for Substance Abuse* (CSAT 1999*a*) at http://www.kap.samhsa.gov/products/manuals/index.htm for specific examples of interview questions.

Most patients are willing and able to provide reliable, factual information regarding their drug use; however, many cannot articulate their reasons or motivation for using drugs. An effective interview should focus on drug use, patterns and consequences of use, past attempts to deal with problems, medical and psychiatric history (the "what, who, when, where, how")—not on the reasons (the "why") for addiction problems. Questions should be asked in a direct and straightforward manner, using simple language and avoiding street terms. Assumptive or quantifiable questions, such as those in figure 3–3, yield more accurate responses in the initial phases of the interview.

Components of the Complete History. A thorough and comprehensive medical, social, and drug use history should be taken on all patients being evaluated for substance

Figure 3–2

Targeted, Open-Ended Questions About Drug and Alcohol Use

- "How has heroin use affected your life?"
- "How has hydrocodone affected your life?"
- "In the past, what factors have helped you stop using?"
- "What specific concerns do you have today?"

Figure 3–3

Quantifiable Interview Questions

- "At what age did you first use alcohol or other drugs?"
- "How many days of the week do you drink alcohol?"
- "How often do you use heroin?"
- "When was the last time you were high?"
- "How many times did you use last month?"

use disorders. The components of a complete history are shown in figure 3–4.

Physical Examination

The physical examination should focus on physical findings related to addiction. Several physical findings may lead the physician to suspect addiction in patients who deny drug use or have equivocal screening results. Figure 3–5 lists physical examination findings that suggest addiction or its complications. The physical complications of opioid addiction should be identified and addressed as part of the overall treatment plan.

Assessing Intoxication and Overdose. It is vitally important to assess for signs of opioid intoxication, overdose, or withdrawal during

Figure 3–4

Components of a Complete Substance Abuse Assessment History

- Substance use history (e.g., age of first use; substances used; change in effects over time; history of tolerance, overdose, withdrawal; attempts to quit; current problems with compulsivity or cravings)
- Addiction treatment history (e.g., previous treatments for addiction, types of treatments tried, outcomes of treatment attempts)
- Psychiatric history (e.g., patient's diagnoses, psychiatric treatments recommended/attempted, outcomes of treatments)
- Family history (e.g., substance use disorders in family, family medical and psychiatric history)
- Medical history (e.g., detailed review of systems, past medical/surgical history, sexual history [for women, determine likelihood of pregnancy], current and past medications, pain history)
- Social history (e.g., quality of recovery environment, family/living environment, substance use by members of support network)
- Readiness to change (e.g., patient's understanding of his or her substance use problem, Stage of Change the patient is in [see appendix G], patient's interest in treatment now, whether treatment is coerced or voluntary)

Figure 3–5

Examination Findings Suggestive of Addiction or Its Complications

- General:
  - Odor of alcohol on breath
  - Odor of marijuana on clothing
  - Odor of nicotine or smoke on breath or clothing
  - Poor nutritional status
  - Poor personal hygiene
- Behavior:
  - Intoxicated behavior during exam
  - Slurred speech
  - Staggering gait
  - Scratching
- Skin:*
  - Signs of physical injury
  - Bruises
  - Lacerations
  - Scratches
  - Burns
  - Needle marks
  - Skin abscesses
  - Cellulitis
  - Jaundice
  - Palmar erythema
  - Hair loss
  - Diaphoresis
  - Rash
  - Puffy hands
- Head, Eyes, Ears, Nose, Throat (HEENT):
  - Conjunctival irritation or injection
  - Inflamed nasal mucosa
  - Perforated nasal septum
  - Blanched nasal septum
  - Sinus tenderness
  - Gum disease, gingivitis
  - Gingival ulceration
  - Rhinitis
  - Sinusitis
  - Pale mucosae
  - Burns in oral cavity
- Gastrointestinal:
  - Hepatomegaly
  - Liver tenderness
  - Positive stool hemoccult
- Immune:
  - Lymphadenopathy
- Cardiovascular:
  - Hypertension
  - Tachycardia
  - Cardiac arrhythmia
  - Heart murmurs, clicks
  - Edema
  - Swelling
- Pulmonary:
  - Wheezing, rales, rhonchi
  - Cough
  - Respiratory depression
- Female reproductive/endocrine:
  - Pelvic tenderness
  - Vaginal discharge
- Male reproductive/endocrine:
  - Testicular atrophy
  - Penile discharge
  - Gynecomastia
- Neurologic:
  - Sensory impairment
  - Memory impairment
  - Motor impairment
  - Ophthalmoplegia
  - Myopathy
  - Neuropathy
  - Tremor
  - Cognitive deficits
  - Ataxia
  - Pupillary dilation or constriction

*For additional information, see the CSAT publication entitled *Classifying Skin Lesions of Injection Drug Users: A Method for Corroborating Disease Risk*, NCADI Order No. AVD 154, DHHS Publication No. (SMA) 02-3753, Printed 2002. Order from: http://store.health.org/.

the physical examination. Opioid overdose should be treated as a medical emergency. Figure 3–6 lists the signs of opioid intoxication and overdose.

Assessing Opioid Withdrawal. Opioid withdrawal can be objectively assessed by using one of the following several instruments:

- COWS (Clinical Opiate Withdrawal Scale) (Wesson et al. 1999)
- SOWS (Short Opiate Withdrawal Scale) (Bradley et al. 1987; Gossop 1990; Handelsman et al. 1987)
- CINA (Clinical Institute Narcotic Assessment Scale for Withdrawal Symptoms) (Peachey and Lei 1988)
- Narcotic Withdrawal Scale (Fultz and Senay 1975)

Full text and/or links to these instruments are included in appendix B. Figure 3–7 shows methods of staging and grading opioid withdrawal.

Assessing Other Drug Intoxication or Withdrawal Syndromes. Instruments for assessing withdrawal from alcohol and benzodiazepines include

- CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol, Revised) (Sullivan et al. 1989)
- CIWA-B (Clinical Institute Withdrawal Assessment for Benzodiazepines) (Busto et al. 1989)

Mental Status Examination

In addition to observing a patient's behavior during history taking and the physical examination, a formal mental status examination (MSE) should be performed, including the components shown in figure 3–8.

Information from the interview and MSE may reveal significant current or past psychiatric problems. Depending on the physician's expertise and comfort in managing

Figure 3–6

Signs of Opioid Intoxication and Overdose

Syndrome	Physical Findings
Opioid Intoxication	Conscious Sedated, drowsy Slurred speech "Nodding" or intermittently dozing Memory impairment Mood normal to euphoric Pupillary constriction
Opioid Overdose	Unconscious Pinpoint pupils Slow, shallow respirations; respirations below 10 per minute Pulse rate below 40 per minute Overdose triad: apnea, coma, pinpoint pupils (with terminal anoxia: fixed and dilated pupils)

Figure 3–7

Staging and Grading Systems of Opioid Withdrawal

Stage	Grade	Physical Signs/Symptoms
Early Withdrawal (8–24 hours after last use)	Grade 1	Lacrimation and/or rhinorrhea Diaphoresis Yawning Restlessness Insomnia
	Grade 2	Dilated pupils Piloerection Muscle twitching Myalgia Arthralgia Abdominal pain
Fully Developed Withdrawal (1–3 days after last use)	Grade 3	Tachycardia Hypertension Tachypnea Fever Anorexia or nausea Extreme restlessness
	Grade 4	Diarrhea and/or vomiting Dehydration Hyperglycemia Hypotension Curled-up position

Figure 3–8

Mental Status Examination Checklist

- General appearance
- Behavior and interaction with interviewer
- Speech and voice
- Motor activity
- Mood and affect
- Perceptions
  - Hallucinations
- Thought process
- Thought content
  - Suicidal ideation
  - Homicidal ideation
  - Delusions
- Insight
- Judgment
- Motivation and readiness to change
  - Patient's stated goals and expectations
- Cognitive function
  - Orientation
  - Memory
  - Attention
  - Concentration
  - Fund of information
  - Literacy skills
  - Abstraction
  - Intelligence
- Personality characteristics
- Defense mechanisms

psychiatric disorders, referral to an addiction psychiatrist or psychologist for a full mental health evaluation and/or formal psychiatric diagnosis may be indicated before starting treatment for addiction.

Laboratory Evaluations

Laboratory testing is an important part of the assessment and evaluation of patients who have an addiction. Laboratory tests cannot make a diagnosis of addiction, but a variety of laboratory evaluations are useful in the comprehensive assessment of patients who have an addiction.

The recommended baseline laboratory evaluation of patients who are addicted to opioids is shown in figure 3–9.

The following additional laboratory evaluations should be considered and offered as indicated:

- Blood alcohol level (using a breath testing instrument or a blood sample)
- Infectious disease evaluation:
  - HIV antibody testing
  - Hepatitis B virus (HBV) and hepatitis C virus (HCV) screens
  - Serology test for syphilis—Venereal Disease Research Laboratories (VDRL)
  - Purified protein derivative (PPD) test for tuberculosis, preferably with control skin tests

In addition, other laboratory evaluations may be indicated by the patient's history or physical examination. Appropriate counseling should be provided, and consent obtained, before testing for certain infectious diseases (e.g., HIV, hepatitis C). Abnormalities or medical problems detected by laboratory evaluation should be addressed as they would be for patients who are not addicted.

Several findings may alert physicians to potential complications to treatment with buprenorphine. Alcohol use may complicate buprenorphine treatment; indirect indicators of excess alcohol use include elevated mean corpuscular volume (MCV) and gamma glutamyl transpeptidase (GGT). Liver enzyme abnormalities also may suggest liver disease from toxicity, infection, or other factors. Additional biomedical markers such as Carbohydrate-Deficient Transferrin (CDT) may provide further objective information on screening and confirmation of acute or recent alcohol consumption, relapse to use, heavy or harmful use, and alcohol-related organ dysfunction. Guidance on liver disease in patients who are addicted to opioids will be available from SAMHSA's Division of Pharmacologic Therapies (DPT) Web site at http://www.dpt.samhsa.gov.

As described elsewhere, pregnancy, HIV treatment, and active hepatitis or liver disease also may complicate treatment with buprenorphine. Pregnant women may not be optimal candidates for buprenorphine treatment. HIV-positive status does not preclude buprenorphine treatment, but as-yet-unrecognized antiretroviral medication interactions with buprenorphine may potentially interfere with treatment. Positive results on hepatitis B surface antigen testing indicate active HBV infection, possibly associated with active hepatitis. Further testing (e.g., serial enzymes) may be indicated to determine whether HBV infection complicates buprenorphine treatment. Hepatitis B information for health professionals can be accessed on the Centers for Disease Control and Prevention (CDC) Web site at http://www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm.

A confirmed positive hepatitis C antibody test indicates current or past infection with HCV. Patients who test positive for HCV

Figure 3–9

Recommended Baseline Laboratory Evaluation of Patients Who Are Addicted to Opioids

- Serum electrolytes
- BUN and creatinine
- CBC with differential and platelet count
- Liver function tests (GGT, AST, ALT, PT or INR, albumin)
- Lipid profile
- Urinalysis
- Pregnancy test (for women of childbearing age)
- Toxicology tests for drugs of abuse
- Hepatitis B and C screens

should be further evaluated and treated according to the most up-to-date recommendations. Training for health professionals on HCV is available on the CDC Web site at http://www.cdc.gov/ncidod/diseases/hepatitis/c_training/edu/default.htm. The 2002 National Institutes of Health (NIH) Consensus Statement regarding the management of hepatitis C is available on the Web at http://consensus.nih.gov/cons/116/116cdc_intro.htm. Materials about hepatitis C also are available on the Agency for Healthcare Research and Quality Web site at http://www.ahrq.gov/clinic/epcsums/hepcsum.htm.

Positive serology tests for syphilis may indicate active or past infection with *Treponema pallidum*. All patients with such positive test results should be treated onsite or referred to a local health department for further evaluation and treatment. It should be noted, however, that biologic false positive results on serology tests for syphilis are common in individuals who abuse drugs intravenously. Only those with confirmatory fluorescent treponemal antibody absorption (FTA-ABS) tests are likely to have actual treponemal infection. The most current treatment recommendations for syphilis and other sexually transmitted diseases (STDs) are posted on the CDC Web site at http://www.cdc.gov/std/.

A positive PPD skin test may indicate past or current infection with tuberculosis. Any patient with a positive PPD test should be referred to a local health department for further evaluation and treatment. Additional information on tuberculosis and its treatment is found on the CDC Web site at http://www.cdc.gov/nchstp/tb/links.htm. Physicians should be familiar with all reporting requirements for infectious diseases in their State.

Evaluations of Drug Use

Tests for illicit drugs are not sufficient to diagnose addiction and cannot substitute for a clinical interview and medical evaluation of the patient (Casavant 2002). Hammett-Stabler et al. (2002) point out that the term *drug screen* is a misnomer, because not all drugs are, and cannot be, tested for routinely. Physicians must decide which drug tests are necessary in each clinical setting, including office-based buprenorphine treatment. Physicians and laboratory personnel must understand the limitations of the assays used, the pharmacokinetic characteristics of the drugs assayed, the parent

compound–metabolite relationships, and how to interpret laboratory results (Hammett-Stabler et al. 2002). Testing for drugs can be performed on a number of bodily fluids and tissues, including urine, blood, saliva, sweat, and hair. Urine screening is the method most commonly employed. A comprehensive discussion of urine drug testing in the primary care setting can be found in *Urine Drug Testing in Primary Care: Dispelling the Myths & Designing Strategies* (Gourlay et al. 2002). When selecting drug tests, physicians should consider the cost to patients, as testing for all possible drugs of abuse can be costly.

In buprenorphine treatment, appropriate tests for illicit drug use should be administered as part of patient assessment. Physicians should explain the role of drug testing at the beginning of treatment for addiction. The literature supports the therapeutic utility of random drug testing in clinical settings (Preston et al. 2002). Laboratory test results can be used in the physician–patient interaction to further treatment objectives, to address patient denial, and to reinforce abstinence from other drugs. Initial and ongoing drug screening should be used to detect or confirm the recent use of drugs (e.g., alcohol, benzodiazepines, barbiturates) that could complicate management of a patient on buprenorphine.

When a patient requests treatment with buprenorphine, a toxicology screen can help to establish that the patient is indeed using either a proscribed substance such as heroin or a prescribed substance such as oxycodone. A negative test does not necessarily mean that the patient is not using an opioid. It may mean that the patient has not used an opioid within a period of time sufficient to produce measurable metabolic products or that the patient was not using the drug for which he or she was tested. Thus, as with any patient, the physician is alerted to a spectrum of possibilities and works with the patient using the information collected from the toxicology screen.

Several manufacturers produce combination urine collection and test kits that facilitate in-office urine testing. In-office testing facilitates prompt evaluation of clinical parameters and allows the physician to present the results to the patient and to make immediate therapeutic use of the information. However, physicians who do not work in a setting with an onsite, federally regulated laboratory must ensure that they are using in-office testing kits waived from regulatory oversight under the Clinical Laboratory Improvement Amendments (CLIA) law of 1988. See the CLIA pages on the Food and Drug Administration (FDA) Web site at http://www.fda.gov/cdrh/clia/cliawaived.html for more information about the law and CLIA-waived point-of-care testing kits. For the current listing of CLIA-waived urine drug tests, refer to the FDA Web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm or search the FDA CLIA database at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm.

Toxicology testing for drugs of abuse that takes place at scheduled visits cannot be truly random; nevertheless, it is clinically worthwhile. Urine samples should be collected in a room where they cannot be diluted or otherwise adulterated and where patients are not permitted to bring briefcases, purses, bags, or containers of any sort. If these conditions are not feasible, temperature-sensitive strips, specific gravity, and creatinine can be used to minimize the possibility of false or adulterated urine specimens. If the physician's office cannot provide this service, patients can be referred to a facility that is equipped to perform monitored specimen collection. Another option that is sometimes feasible is to collect a sample of oral fluid (saliva) to be sent to a laboratory for testing.

Timely shipment of samples for testing and rapid turnaround time for the results are also important issues that should be resolved

before undertaking office-based treatment of opioid addiction. If a patient needs drug test results for employment or for legal monitoring, strict chain-of-custody procedures must be followed, and samples should be evaluated by a SAMHSA-certified laboratory. If a patient subsequently wants to use the drug test result for other purposes, both the physician and the patient should understand the limits of the office testing and other requirements for the test. Other than for U.S. Department of Health and Human Services and U.S. Department of Transportation, private-sector testing requirements may be less rigorous. Further information about the detection of drugs in urine and other biological samples is found in appendix E.

Diagnosis of Opioid-Related Disorders

After a thorough assessment of a patient has been conducted, a formal diagnosis can be made. Criteria for substance dependence, such as those set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) (see Appendix C) or the International Classification of Diseases—Ninth Edition—Clinical Modification (ICD-9-CM), should be used to document a diagnosis of opioid dependence. (This diagnosis is not merely physical dependence on opioids but corresponds to opioid addiction, classically defined as compulsive use despite harm.)

DSM-IV-TR defines several opioid-related disorders. (See figure 3–10.) A DSM-IV-TR diagnosis of either opioid dependence or abuse is based on a cluster of behaviors and physiological effects occurring within a specific timeframe. The diagnosis of opioid dependence always takes precedence over that of opioid abuse (i.e., a diagnosis of abuse is made only if DSM-IV-TR criteria for dependence have never been met). As a general rule, to be considered for buprenorphine maintenance, patients should meet the DSM-IV-TR criteria for a diagnosis of opioid dependence. (See full diagnostic criteria in appendix C.) In rare instances, a patient may be physiologically dependent on opioids and meet DSM-IV-TR criteria for abuse, but

Figure 3–10

DSM-IV-TR Opioid Use Disorders (ICD-9 Code)

- Opioid Abuse (305.50)
- Opioid Dependence (304.00)
- Opioid Intoxication (292.89)
- Opioid Withdrawal (292.0)
- Opioid Intoxication Delirium (292.81)
- Opioid-Induced Psychotic Disorder, With Delusions (292.11)
- Opioid-Induced Psychotic Disorder, With Hallucinations (292.12)
- Opioid-Induced Mood Disorder (292.84)
- Opioid-Induced Sexual Dysfunction (292.89)
- Opioid-Induced Sleep Disorder (292.89)
- Opioid-Related Disorder NOS (292.9)

Source: International Classification of Diseases, 9th Rev., Clinical Modification: ICD-9-CM. Volumes 1 and 2. Salt Lake City, UT; Ingenix, Medicode, 2003. 810 pages.

not for dependence. In such a case, a short course of buprenorphine may be considered for detoxification. Maintenance treatment with buprenorphine is not recommended for patients who do not meet DSM-IV-TR criteria for opioid dependence.

Common Comorbid Medical Conditions

Individuals addicted to opioids may have the same chronic diseases seen in the general population and should be evaluated as appropriate for diseases that require treatment (e.g., diabetes, hypertension). In addition, a number of medical conditions are commonly associated with opioid and other drug addictions. During the course of a medical history and physical examination, the possible existence of these conditions should be evaluated. Refer to figure 3–11 for a detailed list of selected medical disorders related to drug and alcohol use.

Infectious diseases are more common among individuals who are addicted to opioids, individuals who are addicted to other drugs, and individuals who inject drugs. For example, in some areas, more than 50 percent of injection drug users may be HIV positive. There are wide variations in the epidemiology of HIV infection, however, and in other areas the prevalence of HIV infection among injection drug users may be less than 10 percent. Because of the potential impact of HIV on the lives of affected patients and the availability of effective treatments, it is important to screen for HIV infection among patients who present for buprenorphine treatment.

Tuberculosis is also a major problem among substance abusers. In 2001, 2.3 percent of tuberculosis cases in the United States occurred in injection drug users, 7.2 percent in noninjection drug users, and 15.2 percent in individuals with excessive alcohol use in the past 12 months (CDC 2002; http://www.cdc.gov/nchstp/tb/surv/surv2001/default.htm. See tables 28, 29, and 30). Individuals who abuse drugs and alcohol are also at increased risk of engaging in high-risk sexual behavior (e.g., exposure to multiple partners, inconsistent use of safe sexual practices) and of contracting syphilis, gonorrhea, and other STDs.

Among individuals who are opioid addicted, other common medical conditions are related to the use of other drugs and to the life disruptions that often accompany addiction. These conditions include nutritional deficiencies and anemia caused by poor eating habits; chronic obstructive pulmonary disease secondary to cigarette smoking; impaired hepatic function or moderately elevated liver enzymes from various forms of chronic hepatitis (particularly hepatitis B and C) and alcohol consumption; and cirrhosis, neuropathies, or cardiomyopathy secondary to alcohol dependence.

Summary

After completing a comprehensive assessment of a candidate for treatment, the physician should be prepared to

- Establish the diagnosis or diagnoses
- Determine appropriate treatment options for the patient
- Make initial treatment recommendations
- Formulate an initial treatment plan
- Plan for engagement in psychosocial treatment
- Ensure that there are no absolute contraindications to the recommended treatments
- Assess other medical problems or conditions that need to be addressed during early treatment
- Assess other psychiatric or psychosocial problems that need to be addressed during early treatment

The next section describes methods for determining the appropriateness of buprenorphine treatment for patients who have an opioid addiction.

Figure 3–11

Selected Medical Disorders Related to Alcohol and Other Drug Use

Cardiovascular	*Alcohol*: Cardiomyopathy, atrial fibrillation (holiday heart), hypertension, dysrhythmia, masks angina symptoms, coronary artery spasm, myocardial ischemia, high-output states, coronary artery disease, sudden death. *Cocaine*: Hypertension, myocardial infarction, angina, chest pain, supraventricular tachycardia, ventricular dysrhythmias, cardiomyopathy, cardiovascular collapse from body-packing rupture, moyamoya vasculopathy, left ventricular hypertrophy, myocarditis, sudden death, aortic dissection. *Tobacco*: Atherosclerosis, stroke, myocardial infarction, peripheral vascular disease, cor pulmonale, erectile dysfunction, worse control of hypertension, angina, dysrhythmia. *Injection drug use*: Endocarditis, septic thrombophlebitis.
Cancer	*Alcohol*: Aerodigestive (lip, oral cavity, tongue, pharynx, larynx, esophagus, stomach, colon), breast, hepatocellular and bile duct cancers. *Tobacco*: Oral cavity, larynx, lung, cervical, esophagus, pancreas, kidney, stomach, bladder. *Injection drug use or high-risk sexual behavior*: Hepatocellular carcinoma related to hepatitis C.
Endocrine/ Reproductive	*Alcohol*: Hypoglycemia and hyperglycemia, diabetes, ketoacidosis, hypertriglyceridemia, hyperuricemia and gout, testicular atrophy, gynecomastia, hypocalcemia and hypomagnesemia because of reversible hypoparathyroidism, hypercortisolemia, osteopenia, infertility, sexual dysfunction. *Cocaine*: Diabetic ketoacidosis. *Opiates*: Osteopenia, alteration in gonadotropins, decreased sperm motility, menstrual irregularities. *Tobacco*: Graves disease, azoospermia, erectile dysfunction, osteopenia, osteoporosis, fractures, estrogen alterations, insulin resistance. *Any addiction*: Amenorrhea.
Hepatic	*Alcohol*: Steatosis (fatty liver), acute and chronic hepatitis (infectious [that is, B or C] or toxic [that is, acetaminophen]), alcoholic hepatitis, cirrhosis, portal hypertension and varices, spontaneous bacterial peritonitis. *Cocaine*: Ischemic necrosis, hepatitis. *Opiates*: Granulomatosis. *Injection drug use or high-risk sexual behavior*: Infectious hepatitis B and C (acute and chronic) and delta.
Hematologic	*Alcohol*: Macrocytic anemia, pancytopenia because of marrow toxicity and/or splenic sequestration, leukopenia, thrombocytopenia, coagulopathy because of liver disease, iron deficiency, folate deficiency, spur cell anemia, burr cell anemia. *Tobacco*: Hypercoagulability. *Injection drug use or high-risk sexual behavior*: Hematologic consequences of liver disease, hepatitis C-related cryoglobulinemia and purpura.

Figure 3–11

Selected Medical Disorders Related to Alcohol and Other Drug Use, Continued

Infectious	*Alcohol*: Hepatitis C, pneumonia, tuberculosis (including meningitis), HIV, sexually transmitted diseases, spontaneous bacterial peritonitis, brain abscess, meningitis. *Opiates*: Aspiration pneumonia. *Tobacco*: Bronchitis, pneumonia, upper respiratory tract infections. *Injection drug use*: Endocarditis, cellulitis, pneumonia, septic thrombophlebitis, septic arthritis (unusual joints, that is, sternoclavicular), osteomyelitis (including vertebral), epidural and brain abscess, mycotic aneurysm, abscesses and soft tissue infections, mediastinitis, malaria, tetanus. *Injection or high-risk sexual behavior*: Hepatitis B, C, and delta; HIV; sexually transmitted diseases.
Neurologic	*Alcohol*: Peripheral and autonomic neuropathy, seizure, hepatic encephalopathy, Korsakoff dementia, Wernicke syndrome, cerebellar dysfunction, Marchiafava-Bignami syndrome, central pontine myelinolysis, myopathy, amblyopia, stroke, withdrawal, delirium, hallucinations, toxic leukoencephalopathy, subdural hematoma, intracranial hemorrhage. *Cocaine*: Stroke, seizure, status epilepticus, headache, delirium, depression, hypersomnia, cognitive deficits. *Opiates*: Seizure (overdose and hypoxia), compression neuropathy. *Tobacco*: Stroke, small vessel ischemia and cognitive deficits. *Any addiction*: Compression neuropathy.
Nutritional	*Alcohol*: Vitamin and mineral deficiencies (B_1, B_6, riboflavin, niacin, vitamin D, magnesium, calcium, folate, phosphate, zinc). *Any addiction*: Protein malnutrition.
Other Gastrointestinal	*Alcohol*: Gastritis, esophagitis, pancreatitis, diarrhea, malabsorption (because of pancreatic exocrine insufficiency, or folate or lactase deficiency), parotid enlargement, malignancy, colitis, Barrett esophagus, gastroesophageal reflux, Mallory-Weiss syndrome, gastrointestinal bleeding. *Cocaine*: Ischemic bowel and colitis. *Opiates*: Constipation, ileus, intestinal pseudo-obstruction. *Tobacco*: Peptic ulcers, gastroesophageal reflux, malignancy (pancreas, stomach). *Any addiction*: Overdose from body-packing.
Prenatal and Perinatal	*Alcohol*: Fetal alcohol effects and syndrome. *Cocaine*: Placental abruption, teratogenesis, neonatal irritability. *Opiates*: Neonatal abstinence syndrome, including seizures. *Tobacco*: Teratogenesis, low birth weight, spontaneous abortion, abruptio placentae, placenta previa, perinatal mortality, sudden infant death syndrome, neurodevelopmental impairment.
Perioperative	*Alcohol*: Withdrawal, perioperative complications (delirium, infection, bleeding, pneumonia, delayed wound healing, dysrhythmia), hepatic decompensation, hepatorenal syndrome, death. *Cocaine*: Hypersomnia and depression in withdrawal, mimicking of postoperative neurologic complications, complications from underlying drug-induced cardiopulmonary disease. *Opiates*: Withdrawal, inadequate analgesia. *Tobacco*: Pulmonary infection, difficulty weaning, respiratory failure, reactive airways exacerbations.

Figure 3–11

Selected Medical Disorders Related to Alcohol and Other Drug Use, Continued

Pulmonary	*Alcohol*: Aspiration, sleep apnea, respiratory depression, apnea, chemical or infectious pneumonitis. *Cocaine*: Nasal septum perforation, gingival ulceration, perennial rhinitis, sinusitis, hemoptysis, upper airway obstruction, fibrosis, hypersensitivity pneumonitis, epiglottitis, pulmonary hemorrhage, pulmonary hypertension, pulmonary edema, emphysema, interstitial fibrosis, hypersensitivity pneumonia. *Inhalants*: Pulmonary edema, bronchospasm, bronchitis, granulomatosis, airway burns. *Opiates*: Respiratory depression/failure, emphysema, bronchospasm, exacerbation of sleep apnea, pulmonary edema. *Tobacco*: Lung cancer, chronic obstructive pulmonary disease, reactive airways, pneumonia, bronchitis, pulmonary hypertension, interstitial lung disease, pneumothorax. *Injection drug use*: Pulmonary hypertension, talc granulomatosis, septic pulmonary embolism, pneumothorax, emphysema, needle embolization.
Renal	*Alcohol*: Hepatorenal syndrome, rhabdomyolysis and acute renal failure, volume depletion and prerenal failure, acidosis, hypokalemia, hypophosphatemia. *Cocaine*: Rhabdomyolysis and acute renal failure, vasculitis, necrotizing angiitis, accelerated hypertension, nephrosclerosis, ischemia. *Opiates*: Rhabdomyolysis, acute renal failure, factitious hematuria. *Tobacco*: Renal failure, hypertension. *Injection drug use or high-risk sexual behavior*: Focal glomerular sclerosis (HIV, heroin), glomerulonephritis from hepatitis or endocarditis, chronic renal failure, amyloidosis, nephrotic syndrome (hepatitis C).
Sleep	*Alcohol*: Apnea, periodic limb movements of sleep, insomnia, disrupted sleep, daytime fatigue. *Cocaine*: Hypersomnia in withdrawal. *Opiates*: Insomnia. *Tobacco*: Insomnia, increased sleep latency.
Trauma	*Alcohol*: Motor vehicle crash, fatal and nonfatal injury, physical and sexual abuse. *Cocaine*: Death during "Russian Roulette." *Opiates*: Motor vehicle crash, other violent injury. *Tobacco*: Burns, smoke inhalation. *Any addiction*: Sexual and physical abuse.
Musculoskeletal	*Alcohol*: Rhabdomyolysis, compartment syndromes, gout, saturnine gout, fracture, osteopenia, osteonecrosis. *Cocaine*: Rhabdomyolysis. *Opiates*: Osteopenia. *Any addiction*: Compartment syndromes, fractures.

Source: Saitz 2003. Overview of medical and surgical complications. In Graham, A.W.; Schultz, T.K.; Mayo-Smith, M.F.; Ries, R.K.; and Wilford, B.B. (eds.) *Principles of Addiction Medicine*, Third Edition.

Determining Appropriateness for Buprenorphine Treatment

Several issues should be considered in evaluating whether a patient is an appropriate candidate for buprenorphine treatment of opioid addiction in the office or other setting.

First, a candidate for buprenorphine treatment for opioid addiction should have an objectively ascertained diagnosis of opioid addiction (compulsive use of opioids despite harm), otherwise known as opioid dependence as defined in the latest edition of the DSM-IV-TR of the APA (2000). Refer to appendix C for DSM-IV-TR diagnostic criteria for opioid dependence and opioid abuse. In rare instances, a patient may be physiologically dependent on opioids and meet DSM-IV-TR criteria for abuse, but not for dependence. In such a case, a short course of buprenorphine may be considered for detoxification. Maintenance treatment with buprenorphine is not recommended for patients who do not meet DSM-IV-TR criteria for opioid dependence.

Second, a candidate for buprenorphine treatment should, at a minimum

- Be interested in treatment for opioid addiction
- Have no absolute contraindication (i.e., known hypersensitivity) to buprenorphine (or to naloxone if treating with the buprenorphine/naloxone combination)
- Be expected to be reasonably compliant with such treatment
- Understand the risks and benefits of buprenorphine treatment
- Be willing to follow safety precautions for buprenorphine treatment
- Agree to buprenorphine treatment after a review of treatment options

Patients who request treatment with buprenorphine to achieve abstinence from all illicit opioid use should be able to receive this treatment, if it is clinically indicated.

Evaluation Questions

To thoroughly evaluate a patient for appropriateness for opioid addiction treatment with buprenorphine, the physician should ask the following questions:

1. **Does the patient have a diagnosis of opioid dependence?** Candidates for buprenorphine treatment should have a diagnosis of opioid dependence. Buprenorphine treatment is not indicated for other disorders.
2. **Are there current signs of intoxication or withdrawal? Is there a risk for severe withdrawal?** The physician should assess the patient for current signs of intoxication or withdrawal from opioids or other drugs as well as for the risk of severe withdrawal. The risk of severe opioid withdrawal is not a contraindication to buprenorphine treatment. The risk of withdrawal from sedative-hypnotics, however, may initially preclude the use of buprenorphine in an office setting.
3. **Is the patient interested in buprenorphine treatment?** If a patient with opioid addiction has not heard of or presented specifically for buprenorphine treatment, buprenorphine treatment should be discussed as a treatment option.
4. **Does the patient understand the risks and benefits of buprenorphine treatment?** (Refer to chapter 2 and appendix H.) It should be assumed that many patients are unaware that buprenorphine is an opioid, thus they should be so informed. The risks and benefits of buprenorphine treatment should be presented to potential patients, and their understanding of these factors evaluated. Physicians must review the safety, efficacy, side effects, potential treatment duration, and other factors with each patient.

5. **Can the patient be expected to adhere to the treatment plan?** This is a judgment call, based on the patient's past adherence to treatment for addiction or other medical conditions, comorbid psychiatric conditions, psychosocial stability, comorbid substance use disorders, and other factors.
6. **Is the patient willing and able to follow safety procedures?** If a patient is unwilling or unable to follow safety procedures, or is dismissive of them, then that patient is not a good candidate for office-based treatment with buprenorphine.
7. **Does the patient agree to treatment after review of the options?** Buprenorphine treatment is not coercive; the patient must agree to treatment before it is initiated. Treatment options (including no treatment, dose-reduction, abstinence-based treatment, and the variety of medication treatments) and their associated risks and benefits should be reviewed so that patients can make informed decisions about buprenorphine treatment.

> …a candidate for buprenorphine treatment for opioid addiction should have an objectively ascertained diagnosis of opioid addiction…

8. **Can the needed resources for the patient be provided (either onsite or offsite)?** Each patient's needs should be assessed. If the resources that are available onsite or offsite are insufficient for a particular patient, he or she should be referred to an appropriate treatment setting or provider.
9. **Is the patient psychiatrically stable?** Is the patient actively suicidal or homicidal? Has he or she recently attempted suicide or homicide? Do current emotional, behavioral, or cognitive conditions complicate treatment? Patients who have significant untreated psychiatric comorbidity are less-than-ideal candidates for office-based buprenorphine treatment. A full psychiatric assessment is indicated for all patients who have significant psychiatric comorbidity. Psychiatric comorbidity requires appropriate management or referral as part of treatment. It should be noted that the buprenorphine clinical trials reported to date have not included patients maintained on antipsychotic or mood-stabilizing agents (e.g., lithium), and thus there is limited or no information on the potential interactions with these medications.
10. **Is the patient pregnant?** If a patient is pregnant or is likely to become pregnant during the course of treatment, buprenorphine may not be the best choice. (See "Pregnant Women and Neonates" in chapter 5.) Currently, methadone maintenance, when it is available, is the treatment of choice for patients who are pregnant and are opioid addicted.
11. **Is the patient currently dependent on or abusing alcohol?** Patients with alcohol abuse or dependence, whether continuous or periodic in pattern, may be at risk of overdose from the combination of alcohol with buprenorphine. Patients with high-risk or harmful drinking patterns are, therefore, less likely to be appropriate candidates for office-based buprenorphine treatment.
12. **Is the patient currently dependent on or abusing benzodiazepines, barbiturates, or other sedative-hypnotics?** Patients who have sedative-hypnotic abuse or dependence, whether continuous or periodic in pattern, may be at some risk of overdose and death from the combination of sedative-hypnotics with buprenorphine.

13. **What is the patient's risk for continued opioid use or continued problems? Does the patient have a history of multiple previous treatments or relapses, or is the patient at high risk for relapse to opioid use? Is the patient using other drugs?** Several factors may increase a patient's risk for continued use of opioids or continued problems. A patient who is using other (nonopioid) drugs or who has a history of multiple previous treatments or relapses may not be an appropriate candidate for office-based buprenorphine treatment. Physicians should assess the patient's understanding of problems and relapse triggers, as well as his or her skills in managing cravings and controlling impulses to use drugs. Multiple previous attempts at detoxification which were followed by relapse to opioid use, however, are not a contradiction to maintenance with buprenorphine. Rather, such a history is a strong indication for maintenance treatment with pharmacotherapy.

14. **Has the patient had prior adverse reactions to buprenorphine?** Cases of acute and chronic hypersensitivity to Subutex® have been reported both in clinical trials and in the postmarketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex® and Suboxone® use. A history of hypersensitivity to naloxone is a contraindication to Suboxone® use. (Reckitt Benckiser Healthcare [UK] Ltd. et al. 2002).

15. **Is the patient taking other medications that may interact with buprenorphine?** Certain medications (e.g., naltrexone) may be absolutely contraindicated with buprenorphine treatment (see chapter 2) and must be discontinued or changed before starting buprenorphine. If this is not a reasonable clinical alternative, the patient may not be a candidate for buprenorphine treatment. Use of other medications, such as those metabolized by the cytochrome P450 3A4 system (e.g., azoles, macrolide antibiotics, calcium channel blockers, selective serotonin reuptake inhibitors [SSRIs]) may need to be closely monitored when used concurrently with buprenorphine. (See figure 2–3.)

16. **Does the patient have medical problems that are contraindications to buprenorphine treatment? Could physical illnesses complicate treatment?** A complete history and physical assessment must address any medical problems or physical illnesses, and physicians must evaluate the impact of these conditions on buprenorphine treatment.

17. **What kind of recovery environment does the patient have? Are the patient's psychosocial circumstances sufficiently stable and supportive?** Any threats to the patient's safety or treatment engagement should be addressed at the beginning of assessment. Supportive relationships and resources will increase the likelihood of successful treatment.

18. **What is the patient's level of motivation? What stage of change characterizes the patient?** Motivation is a dynamic quality that can be enhanced by treatment providers. Physicians may wish to determine each patient's readiness to change using tools such as the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) (see appendix G) and to make interventions directed to the patient's current stage of change. Highly motivated individuals are more appropriate candidates for office-based buprenorphine treatment.

Figure 3–12 provides a checklist for ascertaining the appropriateness for buprenorphine treatment.

Figure 3–12

Buprenorphine Treatment Checklist

1. Does the patient have a diagnosis of opioid dependence?
2. Are there current signs of intoxication or withdrawal? Is there a risk for severe withdrawal?
3. Is the patient interested in buprenorphine treatment?
4. Does the patient understand the risks and benefits of buprenorphine treatment?
5. Can the patient be expected to adhere to the treatment plan?
6. Is the patient willing and able to follow safety procedures?
7. Does the patient agree to treatment after a review of the options?
8. Can the needed resources for the patient be provided (either on- or offsite)?
9. Is the patient psychiatrically stable? Is the patient actively suicidal or homicidal; has he or she recently attempted suicide or homicide? Does the patient exhibit emotional, behavioral, or cognitive conditions that complicate treatment?
10. Is the patient pregnant?
11. Is the patient currently dependent on or abusing alcohol?
12. Is the patient currently dependent on benzodiazepines, barbiturates, or other sedative-hypnotics?
13. What is the patient's risk for continued use or continued problems? Does the patient have a history of multiple previous treatments or relapses, or is the patient at high risk for relapse to opioid use? Is the patient using other drugs?
14. Has the patient had prior adverse reactions to buprenorphine?
15. Is the patient taking other medications that may interact with buprenorphine?
16. Does the patient have medical problems that are contraindications to buprenorphine treatment? Are there physical illnesses that complicate treatment?
17. What kind of recovery environment does the patient have? Are the patient's psychosocial circumstances sufficiently stable and supportive?
18. What is the patient's level of motivation? What stage of change characterizes this patient?

Patients less likely to be appropriate candidates for office-based treatment are individuals whose circumstances or conditions include or have previously included those listed in figure 3–13.

Cautions and Contraindications for Buprenorphine Treatment

Several medical conditions and medications, as well as concurrent abuse of other drugs and alcohol, necessitate caution or are relative contraindications to buprenorphine treatment.

Seizures

Buprenorphine should be used cautiously in patients who are being treated for seizure disorders. When buprenorphine is used concurrently with antiseizure medications (e.g., phenytoin, carbamazepine, valproic acid, and others), metabolism of buprenorphine and/or the antiseizure medications may be altered. (See figure 2–3.) In addition, the relative risk of interaction between buprenorphine and sedative-hypnotics (e.g., phenobarbital, clonazepam) should be kept in mind. Monitoring for therapeutic plasma levels of seizure medications should be considered.

HIV Treatment

Buprenorphine should be used cautiously in combination with HIV antiretroviral medications that may inhibit, induce, or be metabolized by the cytochrome P450 3A4 enzyme system. (See figure 2–3.) Protease inhibitors inhibit cytochrome P450 3A4. Metabolism of buprenorphine and/or the antiretroviral medications may be altered when they are combined. In some cases, therapeutic blood levels may need to be monitored. Note that this is a caution, not a contraindication; successful treatment of addiction with buprenorphine in HIV-infected patients has been well demonstrated (Berson et al. 2001; Carrieri et al. 2000;

Figure 3–13

Conditions and Circumstances That May Preclude a Patient as a Candidate for Office-Based Buprenorphine Treatment

- Comorbid dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol)
- Significant untreated psychiatric comorbidity
- Active or chronic suicidal or homicidal ideation or attempts
- Multiple previous treatments for drug abuse with frequent relapses (except that multiple previous detoxification episodes with relapse are a strong indication for long-term maintenance treatment)
- Poor response to previous well-conducted attempts at buprenorphine treatment
- Significant medical complications
- Conditions that are outside the area of the treating physician's expertise

McCance-Katz et al. 2001; Moatti et al. 2000).

Hepatitis and Impaired Hepatic Function

Pharmacotherapy with buprenorphine is not contraindicated on the basis of mildly elevated liver enzymes; however, elevated liver enzymes should be appropriately evaluated and monitored frequently. Viral hepatitis (especially infection with HBV or HCV) is common among individuals who abuse opioids and should be evaluated and treated appropriately.

Pregnancy

Buprenorphine is classified by FDA as a Category C agent. Very few studies exist on the use of buprenorphine in pregnant women. If a patient is pregnant or is likely to become pregnant during the course of treatment with buprenorphine, the physician must consider whether buprenorphine is the appropriate treatment and must weigh the risks and benefits of buprenorphine treatment against all the risks associated with continued heroin or other opioid use. In the United States, methadone is the standard of care for pregnant women who are addicted to opioids. (See "Pregnant Women and Neonates" in chapter 5.)

> Although the use of other drugs tends to be a predictor of poor adherence, other drug use is not an absolute contraindication to buprenorphine treatment.

Use of Other Drugs

Buprenorphine is a treatment for opioid addiction, not for addiction to other classes of drugs. Although the use of other drugs tends to be a predictor of poor adherence, other drug use is not an absolute contraindication to buprenorphine treatment. (See below for exceptions.)

Patients should be encouraged to abstain from the use of all nonprescribed drugs while receiving buprenorphine treatment. However, abuse of or dependence on other drugs (e.g., alcohol, cocaine, stimulants, sedative-hypnotics, hallucinogens, inhalants) is common among individuals who are addicted to opioids, and such abuse or dependence may interfere with overall treatment adherence.

Patients who use or abuse more than one substance present unique problems and may need referral to resources outside the office setting for more intensive treatment. Patients should be encouraged to be truthful about their use of all drugs. A recent drug use history and a toxicology screen for drugs of abuse are guides to help assess use, abuse, and dependence on opioids and other drugs. Treatment of patients with more than one addiction problem will depend largely on the physician's level of comfort in treating addiction, the availability of psychosocial support and counseling, and the availability of other forms of addiction treatment. (See "Polysubstance Abuse" in chapter 5.)

Sedative-Hypnotics

The use of sedative-hypnotics (benzodiazepines, barbiturates, and others) is a relative contraindication to treatment with buprenorphine because the combination (especially in overdose) has been reported to be associated with deaths (Reynaud et al. 1998*a*,*b*). The combination of buprenorphine and sedative-hypnotics may increase depression of the central nervous system. If

treatment with buprenorphine and sedative-hypnotics is necessary, the doses of both medications may need to be lowered. Physicians must assess for use, intoxication, and withdrawal from sedative-hypnotics. Unfortunately, the use of certain benzodiazepines and other sedatives may not be detected on routine drug screens. Physicians must determine their laboratory's specific parameters for detection of sedative-hypnotic use.

Alcohol

Because alcohol is a sedative-hypnotic drug, patients should be advised to abstain from alcohol while taking buprenorphine. Rarely are individuals with active, current alcohol dependence appropriate candidates for office-based buprenorphine treatment. (It may be possible to treat such patients through initial, intensive services that effectively detoxify the patient from alcohol while concurrently starting buprenorphine [e.g., in an inpatient or residential setting].)

Patients may present with withdrawal symptoms from other drugs at the same time they are experiencing opioid withdrawal symptoms. Buprenorphine will not control seizures caused by withdrawal from alcohol or other sedative-hypnotic substances. Benzodiazepines and barbiturates, the most commonly used pharmacological treatments for seizures caused by alcohol or other sedative-hypnotic withdrawal, should be used only with caution in combination with buprenorphine because of the increased risk of central nervous system and respiratory depression from the combination.

Summary

Patients who may be good candidates for opioid addiction treatment with buprenorphine are those who have an objective diagnosis of opioid addiction, who have the appropriate understanding of and motivation for buprenorphine treatment, and who do not have medical or psychiatric contraindications to this form of treatment. This chapter has provided information on the questions, cautions, and contraindications that should be considered when determining whether a patient is an appropriate candidate for opioid addiction treatment with buprenorphine. Chapter 4 describes the next steps in providing treatment with buprenorphine for opioid addiction.

4 Treatment Protocols

In This Chapter...

Maintenance Treatment With Buprenorphine

Opioid Detoxification With Buprenorphine

Patient Management

Overview

Office-based treatment of opioid addiction has been unavailable in the United States since the early 1900s. Thus, most U.S. physicians today have little or no experience in the management of opioid addiction. As a consequence, physicians often treat substance-*related* disorders (e.g., infectious diseases) without having the resources to treat the concurrent substance-*use* disorder itself. With the introduction of buprenorphine, office-based physicians now will have the ability to treat both the complications of opioid addiction and opioid addiction itself. (For articles on managing opioid-dependent patients in the office setting, please see Fiellin et al. 2001, 2002; O'Connor et al. 1996, 1998.)

Physicians who use buprenorphine to treat opioid addiction must consider the entire process of treatment, from induction, through stabilization, and then maintenance. At each stage of the process, many different factors must be considered if the physician is to provide comprehensive and maximally effective opioid addiction care. Physicians should conduct a comprehensive assessment to understand the nature of an individual's addiction problem, especially with regard to the primary type of opioid abused. Before initiating buprenorphine treatment, physicians should obtain a signed release of information (see Title 42, Part 2 of the Code of Federal Regulations [42 C.F.R. Part 2]) from patients who are currently enrolled in Opioid Treatment Programs (OTPs) or other programs (42 C.F.R. Part 2 2001). (See "Confidentiality and Privacy" in chapter 6.) This chapter provides detailed protocols on the use of buprenorphine for the treatment of opioid addiction. The chapter begins with a discussion of some general issues regarding treatment with buprenorphine.

Buprenorphine Monotherapy and Combination Buprenorphine/Naloxone Treatment

The consensus panel recommends that the buprenorphine/naloxone combination be used for induction treatment (and for stabilization and maintenance) for most patients. However, pregnant women who are determined to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy. In addition, patients who desire to change from long-acting opioids (e.g., methadone, levo-alpha-acetyl-methadol [LAAM]) to buprenorphine should be inducted using buprenorphine monotherapy.* If the buprenorphine monotherapy formulation is elected for induction treatment, it is recommended that patients who are not pregnant be switched to the buprenorphine/naloxone combination form as early in treatment as possible to minimize the possibility of diversion of Subutex® to abuse via the injection route. When the buprenorphine monotherapy formulation is used for induction, it is recommended that it be used for no more than 2 days before switching to the buprenorphine/naloxone combination formulation (for patients who are not pregnant). If buprenorphine alone is to be used for extended periods, the number of doses to be prescribed should be limited, and the use of the monotherapy formulation should be justified in the medical record.

> The consensus panel recommends that the buprenorphine/naloxone combination be used for induction treatment…for most patients.

Although controlled trials have not compared buprenorphine monotherapy to the buprenorphine/naloxone combination for induction, clinical experience in office-based trials conducted by the National Institute on Drug Abuse (NIDA) has demonstrated that physicians were comfortable starting patients on either the monotherapy formulation or the combination formulation and did not report adverse events when patients began directly on combination treatment. Physicians will need to find their own comfort level with the induction protocols, but the consensus panel sees no contraindication to the use of the buprenorphine/naloxone combination in the initiation of buprenorphine treatment, except as noted above.

Opioid Withdrawal Syndrome With Buprenorphine Induction

Because buprenorphine (and particularly buprenorphine/naloxone) can precipitate an opioid withdrawal syndrome if administered to a patient who is opioid dependent and whose receptors are currently occupied by opioids, a patient should no longer be intoxicated or have any residual opioid effect from his or her last dose of opioid before receiving a first dose of buprenorphine.

Due to this required abstinence before initiating buprenorphine treatment, it is likely that patients will feel that they are experiencing the early stages of withdrawal when they present for buprenorphine induction treatment, unless they are on maintenance treatment with a long-acting opioid agonist

*Due to a number of factors, including the association of LAAM with cardiac arrhythmias in some patients, as of January 1, 2004, the sole manufacturer has ceased production of the drug.

(e.g., methadone). If a patient has early symptoms of withdrawal, then the opioid receptors are unlikely to be occupied fully; precipitated withdrawal from administration of buprenorphine will be avoided, and the efficacy of buprenorphine in alleviating withdrawal symptoms can be assessed more easily.

Withdrawal symptoms can occur if either too much or too little buprenorphine is administered (i.e., *spontaneous withdrawal* if too little buprenorphine is given, *precipitated withdrawal* if buprenorphine is administered while the opioid receptors are occupied to a high degree by an opioid agonist). Therefore, physicians must be careful when timing initiation of buprenorphine induction. Each patient's history and concerns must be considered carefully, and patient counseling about potential side effects from buprenorphine overdosing (especially in combination with benzodiazepines) or underdosing (e.g., a reemergence of opioid craving) must be emphasized. Before undertaking buprenorphine treatment of opioid addiction, physicians should be familiar with the signs, symptoms, and time course of the opioid withdrawal syndrome. (See figure 3–7.)

Method of Administration

Buprenorphine sublingual tablets should be placed under the tongue until they are dissolved. For doses requiring the use of more than two tablets, patients should either place all the tablets at once or alternatively, if they cannot fit in more than two tablets comfortably, place two tablets at a time under the tongue. Either way, the tablets should be held under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the medication. Dissolution rates vary, but, on average, the sublingual tablets should dissolve in approximately 5–10 minutes.

Treatment Approach

There are two general approaches to the medication-assisted treatment of opioid addiction: (1) opioid maintenance treatment, and (2) medically supervised withdrawal (detoxification) with either opioid (e.g., methadone) or nonopioid (e.g., clonidine) medications. Because opioid-assisted maintenance and medically supervised withdrawal treatments have not been available outside the OTP setting, many patients may not be aware that these forms of treatment are now available in new clinical settings. Thus, a discussion with patients of all available treatment options is essential.

For many patients, it may be inappropriate to decide arbitrarily on the length of treatment at initial evaluation. It is more likely that patients will need to be started in treatment within a flexible timeframe that responds to the progress and needs of the patient. For example, in one report of rapid-term opioid detoxification using buprenorphine, it was noted that 25 percent of patients initially requesting detoxification subsequently switched to maintenance treatment within the 10-day study (Vignau 1998). Thus, as treatment progresses, it may become a more appropriate time to assess the duration of various aspects of treatment, including medications, counseling therapies, and self-help groups. Therefore, it is important to assess initially, and to reassess periodically, a patient's motivation for treatment, as well as his or her willingness to engage in appropriate counseling and/or a structured rehabilitation program. (See "Assessment" in chapter 3.)

Maintenance Treatment With Buprenorphine

The three phases of maintenance treatment with buprenorphine for opioid addiction are (1) induction, (2) stabilization, and (3) maintenance. The following sections describe these phases.

Induction Phase

Buprenorphine induction (usual duration approximately 1 week), the first phase of

treatment, involves helping a patient begin the process of switching from the opioids of abuse to buprenorphine. The goal of the induction phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no withdrawal symptoms, minimal or no side effects, and no uncontrollable cravings for drugs of abuse. The physician should assess for signs and symptoms of withdrawal or inadequate dosing during induction. Patients should be advised to avoid driving or operating other machinery until they are familiar with the effects of buprenorphine and their dose is stabilized. Induction protocols differ, depending on the type of opioid to which the patient is addicted (e.g., short- or long-acting) and whether or not the patient is in active withdrawal at the time of induction.

The consensus panel recommends that physicians administer initial induction doses as observed treatment (e.g., in the office); further doses may be provided via prescription thereafter. This ensures that the amount of buprenorphine located in the physician's office is kept to a minimum. Following the initial buprenorphine dose, patients should be observed in the physician's office for up to 2 hours. For patients who do not experience excessive opioid agonist symptoms after the initial dose, induction protocols can be followed as described below.

Induction Days 1 and 2: Who Is the Patient and What Does He or She Need?

It is important to identify the opioid(s) that patients have been using, as the response to buprenorphine treatment in individuals dependent on long-acting opioids is different than that seen with short-acting opioids and, therefore, the appropriate induction protocol must be chosen. Most patients starting buprenorphine induction will be physically dependent on a short-acting opioid (e.g., heroin, oxycodone, hydrocodone) and should be in the early stages of withdrawal at the time they receive their first dose of buprenorphine. (See figure 4–1 and appendix B.)

Patients Dependent on Short-Acting Opioids

Before the initial buprenorphine induction dose is administered to a patient dependent on short-acting opioids, a minimum of 12–24 hours should have elapsed since the last use of opioids. The patient should preferably be exhibiting early signs of opioid withdrawal (e.g., sweating, yawning, rhinorrhea, lacrimation). (See figure 3–7.) Patients who are not in active withdrawal because they have not abstained from using opioids for a sufficient period should receive a careful explanation of the advantages of waiting and should be urged to wait until they begin to experience the symptoms of withdrawal.

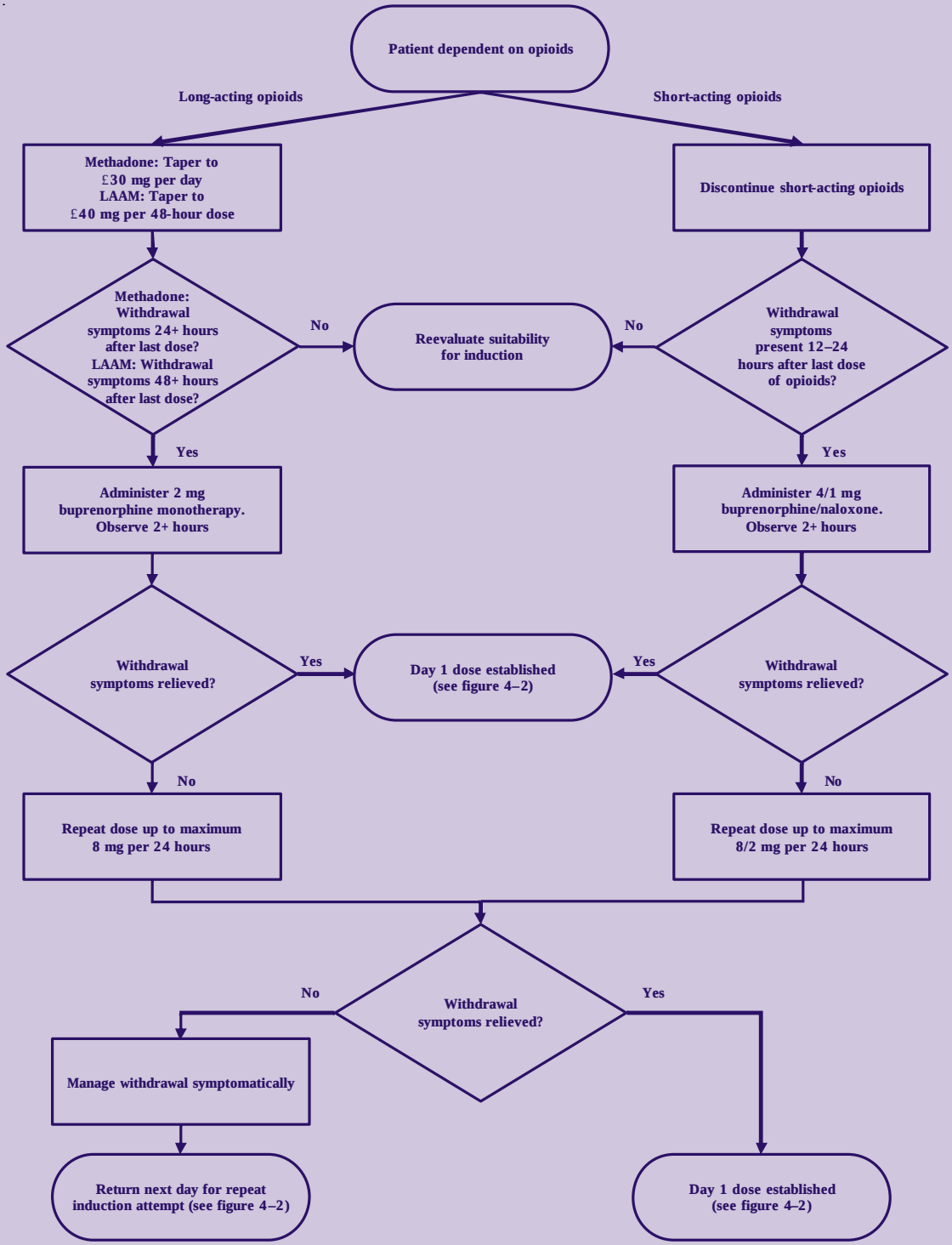
Patients who are experiencing objective signs of opioid withdrawal and whose last use of a short-acting opioid was more than 12–24 hours prior to the initiation of induction can receive a first dose of 4/1–8/2 mg of the buprenorphine/naloxone combination (buprenorphine monotherapy for pregnant women). (See figure 4–1.) If the initial dose of the buprenorphine/naloxone combination is 4/1 mg and opioid withdrawal symptoms subside but then return (or are still present) after 2 hours, a second dose of 4/1 mg can be administered. The total amount of buprenorphine administered in the first day should not exceed 8 mg.

Patients Dependent on Long-Acting Opioids

Induction onto buprenorphine from long-acting opioids (e.g., methadone, LAAM) may be complicated and is best managed by physicians experienced with this procedure. If this treatment will be conducted in an office-based setting, the physician's office must contact the patient's OTP (after receiving signed consent) to determine the methadone or LAAM dosage levels and time of last dose. Such contact will ensure that the physician knows the exact quantity and time of the last methadone or LAAM dose, as well as prevent patients from receiving opioid agonist treatment (OAT) and office-based

Figure 4–1

Induction Days 1–2



buprenorphine treatment simultaneously. To allow this exchange of addiction treatment information per Federal confidentiality regulation 42 C.F.R. Part 2 (see "Confidentiality and Privacy" in chapter 6), the patient must provide signed consent to both the OTP and the buprenorphine-treating physician.

For patients taking methadone, the methadone dose should be tapered to 30 mg or less per day for a minimum of 1 week before initiating buprenorphine induction treatment. Patients should not receive buprenorphine until at least 24 hours after the last dose of methadone. The first dose of buprenorphine should be 2 mg of the monotherapy formulation. (See figure 4–1.) If a patient develops signs or symptoms of withdrawal after the first dose, a second dose of 2 mg should be administered and repeated, if necessary, to a maximum of 8 mg buprenorphine on Day 1.

It should be noted that not all patients maintained on methadone may be good candidates for the switch to buprenorphine treatment at a methadone dose of 30 mg/day. As a methadone taper approaches 30 mg/day many patients become uncomfortable, develop withdrawal symptoms, and are at increased risk of relapse to opioid abuse. Such patients may request the transfer to buprenorphine at higher daily doses of methadone. The decision to transfer a patient to buprenorphine at higher daily methadone doses should be based on clinician judgment, informed by the patient's subjective and objective findings. While there have been case reports of transferring patients to buprenorphine from methadone doses as high as 80 mg/day, there is insufficient data to formulate recommendations regarding which patients may be able to tolerate a switch at these higher doses or the best way to manage the transfer.

No clinical experience with inducting patients from LAAM to buprenorphine is documented. However, extrapolating from consensus panel members' experience with such patients, the panel recommends that the dose of LAAM be tapered down to 40 mg or less per 48-hour dose, and buprenorphine induction should not be undertaken until at least 48 hours after the last dose of LAAM. Induction should then proceed in the same manner and at the same dosage levels as recommended for methadone patients.

Induction Management When Withdrawal Symptoms Are Not Relieved by 8 mg Buprenorphine in the First 24 Hours

If withdrawal symptoms are still not relieved after a total of 8 mg of buprenorphine on Day 1, symptomatic relief with nonopioid medications should be provided and the patient asked to return the following day for dose management. (See "Induction Day 2 and Forward" below.)

Patients Not Physically Dependent on Opioids

Patients who are not physically dependent on opioids but who have a known history of opioid addiction, have failed other treatment modalities, and have a demonstrated need to cease the use of opioids, may be candidates for buprenorphine treatment. Patients in this category will be the exception rather than the rule, however. Other patients in this category would be those recently released from a controlled environment who have a known history of opioid addiction and a high potential for relapse.

Patients who are not physically dependent on opioids should receive the lowest possible dose (2/0.5 mg) of buprenorphine/naloxone for induction treatment.

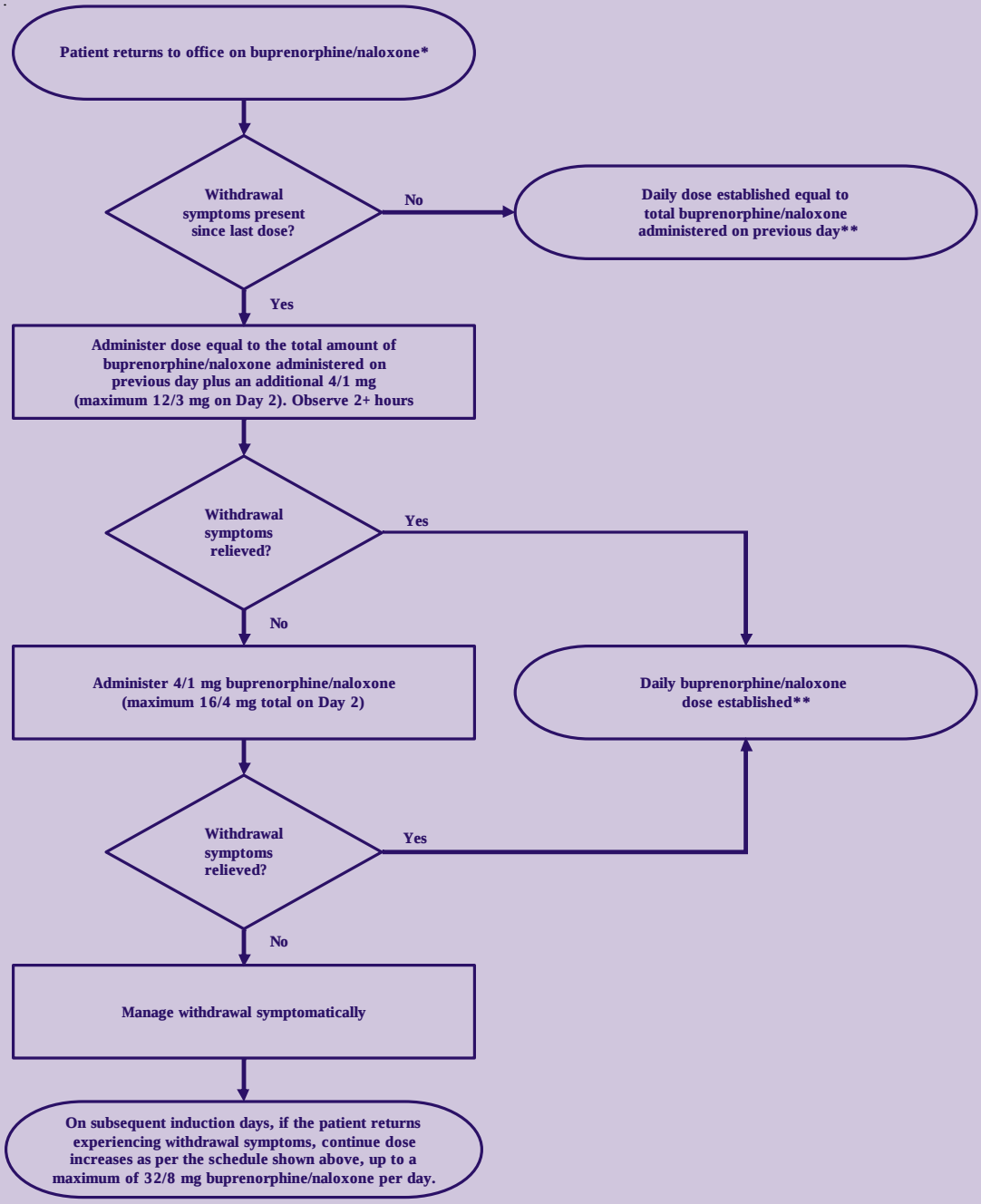
Induction Day 2 and Forward

If buprenorphine monotherapy was administered on Day 1, switch to buprenorphine/naloxone on Day 2 (for a patient who is not pregnant).

For patients who do not experience any difficulties with the first day of buprenorphine dosing, and who are not experiencing withdrawal symptoms on Day 2, the induction schedule shown in figure 4–2 can be followed. The daily buprenorphine/naloxone dose is

Figure 4–2

Induction Day 2 Forward



*If buprenorphine monotherapy was administered on Day 1, switch to buprenorphine/naloxone on Day 2 (for a patient who is not pregnant).

**Dose may be increased by 2/0.5–4/1 mg increments on subsequent days as needed for symptom relief. Target dose of 12/3–16/4 mg buprenorphine/naloxone per day by the end of the first week.

established as equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on Day 1. Doses may be subsequently increased in 2/0.5 to 4/1 mg increments each day, if needed for symptomatic relief, with a target dose of 12/3 to 16/4 mg per day to be achieved within the first week, unless side effects occur. If side effects occur, the dose of buprenorphine should be maintained or lowered until these side effects disappear.

Patients who return on Day 2 experiencing withdrawal symptoms should receive an initial dose of buprenorphine/naloxone equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) administered on Day 1 plus an additional 4/1 mg (maximum initial dose of 12/3 mg). If withdrawal symptoms are still present 2 hours after the dose, an additional 4/1 mg dose can be administered. The total dose on Day 2 should not exceed 16/4 mg. Continue dose increases on subsequent days according to the induction schedule shown in figure 4–2 up to a maximum of 32/8 mg per day.

If patients have problems adjusting to buprenorphine (e.g., experience withdrawal symptoms or continue to feel compelled to use illicit drugs), the dose may need to be increased more rapidly, or to a higher maintenance dose level, and patients may need intensive psychosocial treatments to help them cease illicit use. Patients who continue to take illicit opioids should be warned strongly of the dangers of continuing to do so. Physicians also should verify that patients are taking the medication correctly and should assess the timing of doses in relation to last opioid use, amount of time the medication is allowed to dissolve under the tongue, and dose taken. If a dose of buprenorphine makes a patient feel worse, it is likely that the medication is causing precipitated withdrawal. In this situation, the physician should help the patient to decrease the use of the illicit opioid while gradually increasing the dose of buprenorphine. Toxicology testing for drugs of abuse may be helpful in determining adequacy of clinical response.

Stabilization Phase

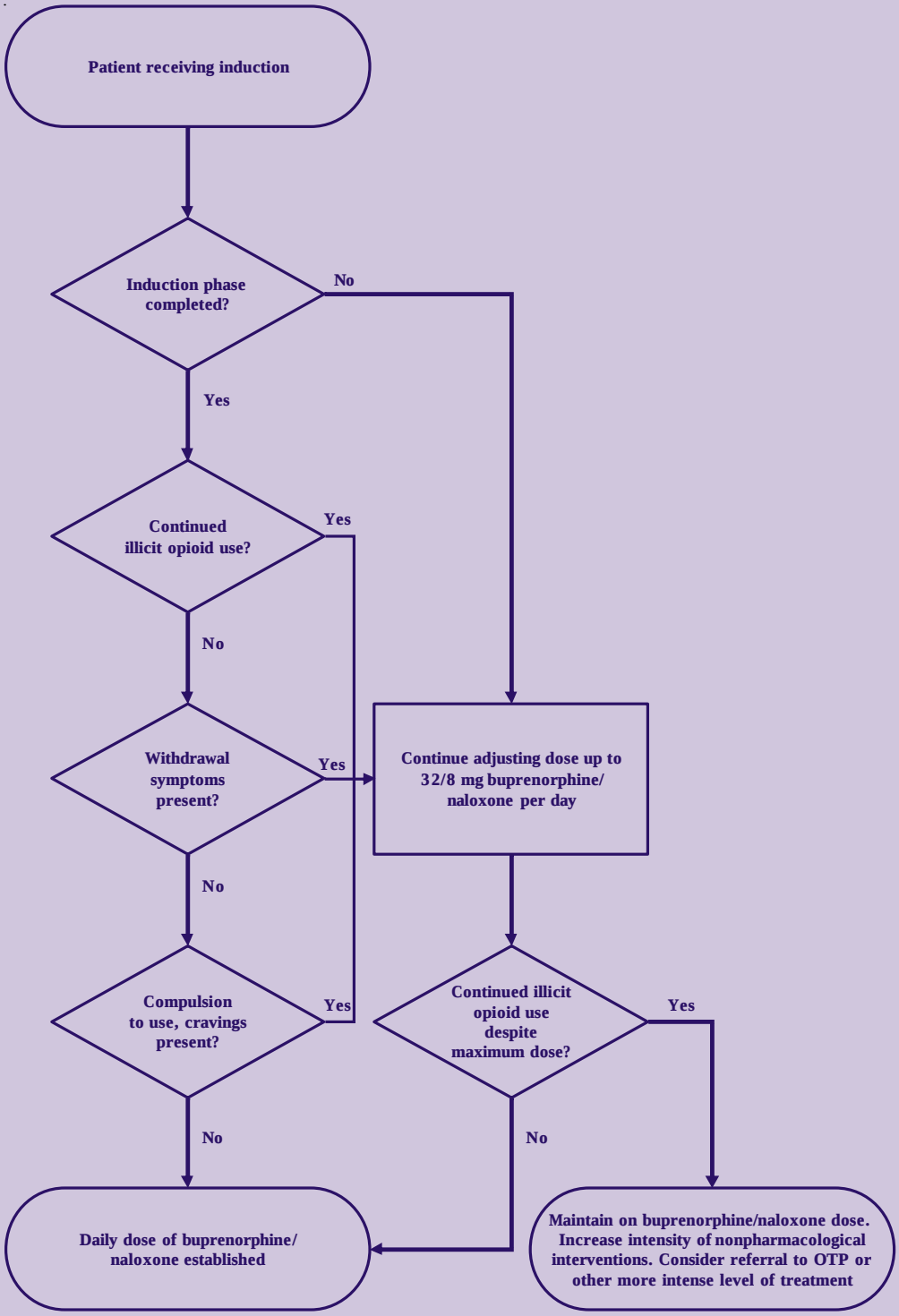
The induction phase is completed and the stabilization phase (usual duration approximately 1 to 2 months) is begun when the patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists. (See figure 4–3.) As with any pharmacotherapy, the goal of buprenorphine treatment is to treat with the minimum dose of medication needed to address target signs, symptoms, desired benefits, and laboratory indices while minimizing side effects. Elimination of objective evidence of opioid use (negative toxicology) represents the key target sign for which to strive. The goal is to reduce self-reported cravings and self-reported use of illicit opioids. One benefit worth achieving is a self-reported increase in opioid blockade such that self-administered illicit opioids induce little or no euphoria. A reduction in opioid-positive toxicology specimens confirms a successful direction in treatment.

Dosage adjustments may be necessary during early stabilization, and frequent contact with patients increases the likelihood of compliance. Until full stabilization is achieved, weekly assessments of patients may be indicated to make necessary dosage adjustments. With stabilization goals in mind, doses of buprenorphine/naloxone may be increased in 2/0.5–4/1 mg increments per week until stabilization is achieved. Nearly all patients will stabilize on daily doses of 16/4–24/6 mg; some, however, may require up to 32/8 mg daily.

Some patients may prefer or may respond better to less-than-daily dosing regimens of buprenorphine. It is possible that less-than-daily dosing will most likely be advantageous in an OTP or other directly observed dose setting, where daily visits might otherwise be required. A variety of studies have shown the efficacy of alternate-day or thrice-weekly buprenorphine administration (Amass et al. 2000; Bickel et al. 1999; Perez de los Cobos et al. 2000; Petry et al. 1999). The typical method of determining the dose for less-than-daily dosing regimens was to double (for

Figure 4–3

Stabilization Phase



alternate-day dosing) or triple (for every-third-day dosing) the stable daily dose for the patient. Although all regimens were determined to be safe and, in most cases, effective, several authors noted that some subjects were more likely to have urine samples positive for opioids on the less-than-daily dosing regimens. During induction and early stabilization daily dosing is recommended.

If a patient continues to use illicit opioids despite the maximal treatment available in the physician's clinical setting, the physician should consider referral to a more intensive therapeutic environment.

Maintenance Phase

The longest period that a patient is on buprenorphine is the period of maintenance. This period may be indefinite. It is easy for physicians to lessen their vigilance during this period, but significant considerations still must be addressed. Attention must be maintained to the psychosocial and family issues that have been identified during the course of treatment. Other issues that will need continual monitoring are related to cravings for opioids and to preventing relapse. Some other issues related to opioid abuse that need to be addressed during maintenance treatment include, but are not limited to, the following:

- Psychiatric comorbidity
- Somatic consequences of drug use
- Family and support issues
- Structuring of time in prosocial activities
- Employment and financial issues
- Legal consequences of drug use
- Other drug and alcohol abuse

The frequent presence of some or all of these problems underscores the importance of providing nonpharmacological services to address comprehensively the needs of patients and to maximize the chances of the best possible outcomes.

Long-Term Medication Management

The design of long-term treatment depends in part on the patient's personal treatment goals and in part on objective signs of treatment success. Maintenance can be relatively short-term (e.g., <12 months) or a lifetime process. Treatment success depends on the achievement of specific goals that are agreed on by both the patient and the physician. Following successful stabilization, decisions to decrease or discontinue buprenorphine should be based on a patient's desires and commitment to becoming medication-free, and on the physician's confidence that tapering would be successful. Factors to be considered when determining suitability for long-term medication-free status include stable housing and income, adequate psychosocial support, and the absence of legal problems. For patients who have not achieved these indices of stabilization, a longer period of maintenance, during which they work through any barriers that exist, may be appropriate. Data suggest that longer duration of medication treatment is associated with less illicit drug use and fewer complications.

Opioid Detoxification With Buprenorphine

This section discusses the use of buprenorphine for the medically supervised withdrawal (detoxification) from short-acting opioids and from OAT with methadone or LAAM. The goal of medically supervised withdrawal from opioids is to provide a smooth transition from a physically dependent to a physically nondependent state. A patient can then engage in further rehabilitation with or without the use of opioid antagonist treatment to assist in relapse prevention. Before considering the use of buprenorphine for withdrawal from illicit opioids or to discontinue OAT, a patient's appropriateness as a candidate for withdrawal or cessation must be determined at the time of assessment. Withdrawal treatment must be

followed by long-term drug-free, or naltrexone, treatment in order to minimize the risk of relapse to opioid abuse. It should be noted, however, that absent a compelling need for the complete avoidance of all opioids, long-term maintenance treatment with buprenorphine is to be preferred in most instances to any form of detoxification or withdrawal treatment.

Buprenorphine for Detoxification From Short-Acting Opioids

Detoxification in patients addicted to short-acting opioids is only a part of the overall approach to treatment. The purpose of using buprenorphine for detoxification from short-acting opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms (and avoiding side effects of buprenorphine).

Induction Phase

The consensus panel recommends that patients dependent on short-acting opioids be inducted directly onto buprenorphine/naloxone tablets. Before initiating buprenorphine induction, patients should have discontinued the use of illicit opioids and should be exhibiting the early symptoms of withdrawal. An initial 4/1 mg dose of buprenorphine/naloxone is recommended. This dose can be followed in 2–4 hours with a second dose of 4/1 mg, if indicated. Over the next 2 days, the dose of buprenorphine/naloxone should be increased to 12/3–16/4 mg per day. The objectives of induction should be to stabilize the patient as rapidly as possible, to minimize any withdrawal symptoms, and to eliminate further use of illicit opioids. Only after a patient has completely discontinued use of illicit opioids should the dose-reduction phase begin. Unless a patient is in a controlled environment (e.g., a hospital or residential setting), cessation of opioid use should be documented with a negative toxicology test for illicit opioids. If a patient is unable to discontinue illicit opioid use, as documented by negative toxicology results, a further period of stabilization or maintenance should be considered. (See figure 4–4.)

Dose Reduction Phase

Long-Period Reduction. The literature suggests that the use of buprenorphine for gradual detoxification over long periods is probably more effective than its use for rapid detoxification over short or moderate periods; however, little research has been conducted on this use of buprenorphine. Patients who are unwilling or unable to engage actively in rehabilitation services without agonist support may not be appropriate candidates for short-term detoxification; however, such patients may benefit from long-term detoxification (or, even more so, from maintenance treatment).

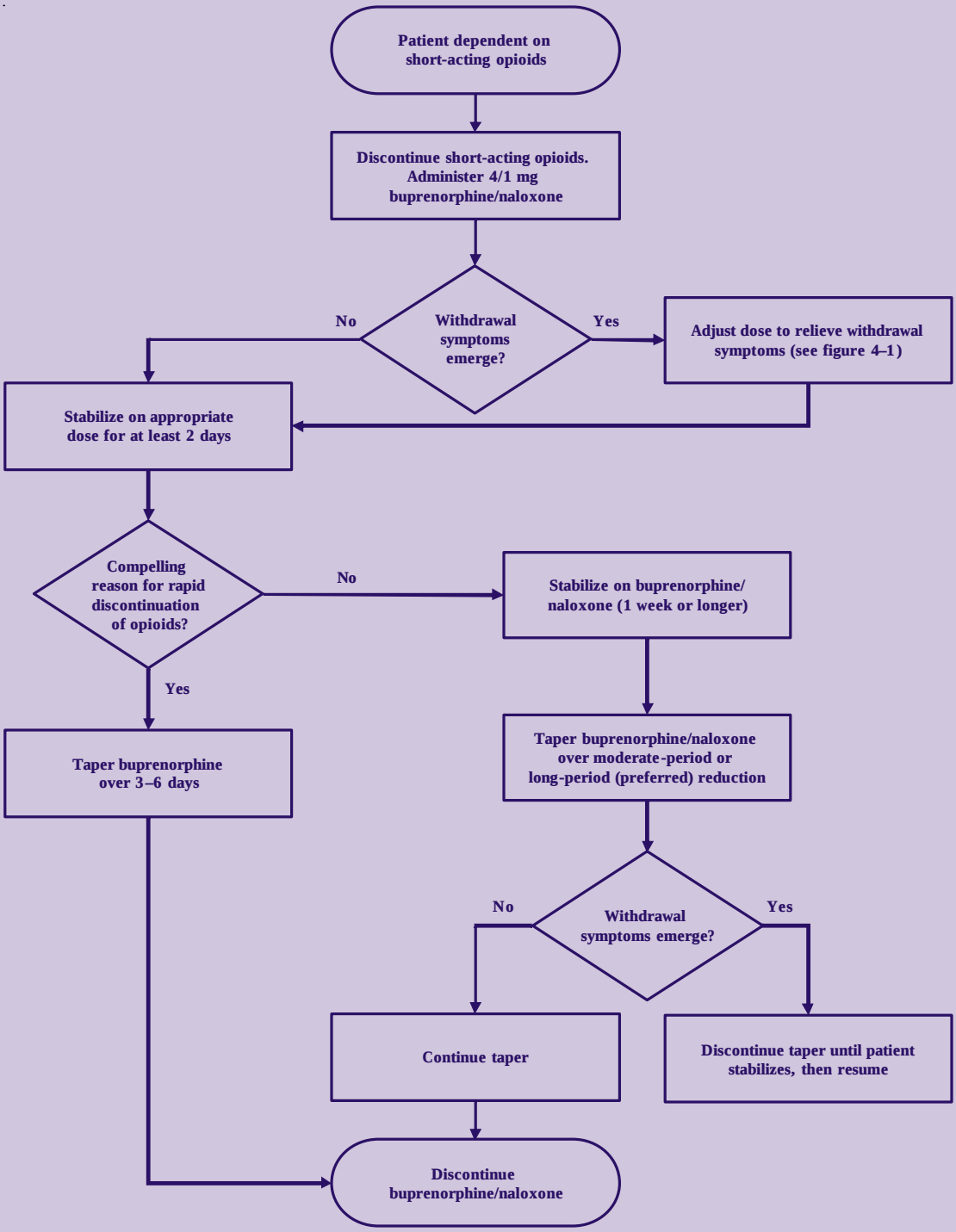
Moderate-Period Reduction. Patients without a compelling need to undergo short-term detoxification, but with a desire to become opioid free and to engage in rehabilitation aimed at an opioid-free lifestyle, can be detoxified over a 10- to 14-day (or longer) period by gradually decreasing the initial stabilization dose of buprenorphine (usually 8–16 mg per day) by 2 mg every 2–3 days. It is extremely important that patients engage in rehabilitation programs during the detoxification period and that they remain engaged in such programs after the conclusion of the detoxification protocol.

> Withdrawal treatment must be followed by long-term drug-free, or naltrexone, treatment in order to minimize the risk of relapse to opioid abuse.

Short-Period Reduction. Patients with a compelling reason to achieve an opioid-free state quickly (e.g., impending incarceration, foreign travel, job requirement) may have

Figure 4–4

Detoxification From Short-Acting Opioids



their buprenorphine dose reduced over 3 days and then discontinued. When compared to clonidine for the treatment of short-term opioid withdrawal, buprenorphine is better accepted by patients and more effective in relieving withdrawal symptoms (Cheskin et al. 1994). Relapse rates and long-term outcomes from such rapid opioid withdrawal using buprenorphine have not been reported, however. Studies of other withdrawal modalities have shown that such brief withdrawal periods are (1) unlikely to result in long-term abstinence and (2) produce minimal, if any, long-term benefits in the treatment of patients dependent on opioids.

Buprenorphine for Discontinuation of OAT

The use of buprenorphine (either as buprenorphine monotherapy or as buprenorphine/naloxone combination treatment) to taper off OAT with methadone or LAAM should be considered only for those patients who have evidence of sustained medical and psychosocial stability. Requests to provide pharmacological withdrawal with buprenorphine or buprenorphine/naloxone should be entertained with caution. Only a small proportion of patients who have achieved stability with OAT are likely to maintain abstinence without medication. Ideally, this decision would be made in conjunction, and in coordination, with a patient's OTP. The option of continued maintenance with buprenorphine/naloxone if withdrawal proves unsuccessful should be discussed.

The guidelines in figure 4–5 describe both short-period (3-day) and moderate-period (2-week) discontinuation of OAT with buprenorphine. Short-period discontinuation is not recommended unless there is a compelling need for rapid discontinuation.

Compelling reasons for discontinuing OAT within a relatively short timeframe might include impending incarceration, foreign travel, conditions of employment, or other circumstances expected to preclude the patient from continuing OAT.

Methadone Discontinuation

In general, patients who are clinically stable and are being slowly tapered off methadone maintenance treatment experience little difficulty until the daily methadone dose reaches 30 mg or less. As the daily dose drops below 30 mg, opioid withdrawal symptoms often emerge between methadone doses. Additionally, the euphoria-blocking and anticraving effects of methadone are much diminished at this low dose level.

LAAM Discontinuation

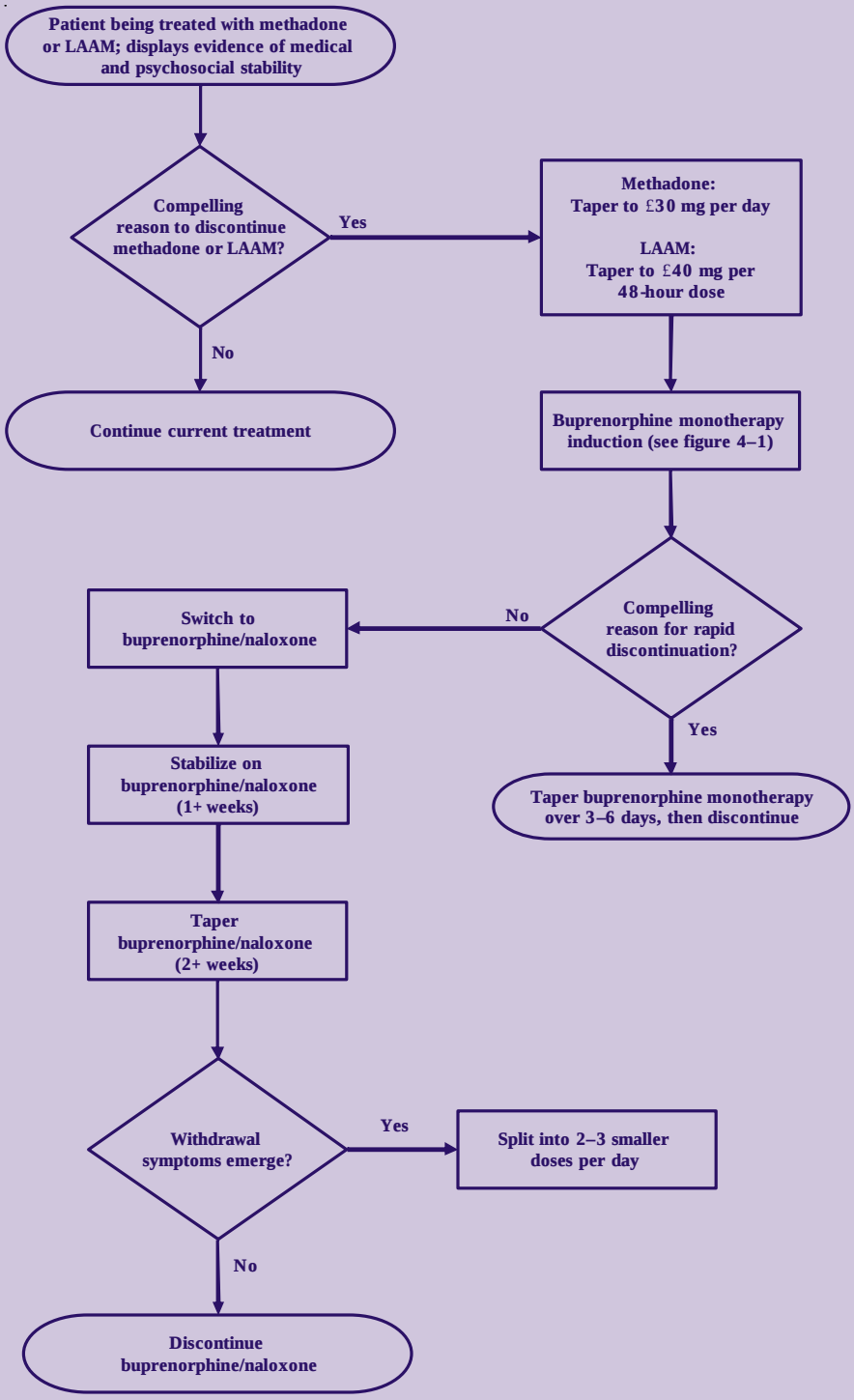
Cessation of OAT with LAAM follows a protocol similar to that for methadone cessation. Patients previously stabilized on LAAM may be candidates for buprenorphine once the LAAM dose is tapered to 40 mg or less per 48 hour dose. At this point, buprenorphine monotherapy can be instituted similarly to procedures for methadone discontinuation, although LAAM's pharmacology must be taken into account. (See figure 4–5.) When the patient has been stabilized on buprenorphine monotherapy, the physician should employ the same decision process described above for methadone discontinuation. If there is a compelling reason for OAT discontinuation, short-term discontinuation with buprenorphine monotherapy can be achieved with a 3-day protocol as described above. In the absence of a compelling reason, the patient should be switched to buprenorphine/naloxone combination treatment, which can be reduced subsequently and eventually discontinued if the patient remains clinically stable without evidence of illicit opioid use. Physicians should remember that patients are most likely to relapse during or after discontinuation. Therefore, patients should be monitored closely for relapse to illicit opioid use, and the dose of buprenorphine should be increased in response to cravings or withdrawal symptoms.

Discontinuation of Buprenorphine/Naloxone

When the decision is made to discontinue buprenorphine/naloxone combination treatment, the daily dose should be decreased

Figure 4–5

Discontinuation of OAT Using Buprenorphine



gradually over a predetermined period or at a rate negotiated by the patient and the physician together. Withdrawal symptoms may emerge as the buprenorphine/naloxone dose is decreased. In this event, the taper may be temporarily suspended.

As with the protocols described above, discontinuation of buprenorphine/naloxone combination treatment may be performed over short periods (e.g., 3 days), but this approach should be used only in the presence of a compelling urgency to discontinue buprenorphine/naloxone in this manner; discontinuation over a longer period is the preferred manner.

Patient Management

Psychosocial Treatment Modalities and Adjuncts

Pharmacotherapy alone is rarely sufficient treatment for drug addiction (McLellan et al. 1993). Treatment outcomes demonstrate a dose-response effect based on the level or amount of psychosocial treatment services that are provided. Therefore, physicians have an additional level of responsibility to patients with opioid addiction problems; this responsibility goes beyond prescribing and/or administering buprenorphine. For most patients, drug abuse counseling—individual or group—and participation in self-help programs (e.g., Alcoholics Anonymous [AA]; Narcotics Anonymous [NA]; Methadone Anonymous, a 12-Step group that supports recovery concurrent with OAT; Self Management and Recovery Training [SMART] Recovery; or Moderation Management) are considered necessary. Self-help groups may be beneficial for some patients and should be considered as one adjunctive form of psychosocial treatment. It should be kept in mind, however, that the acceptance of patients who are maintained on medication for opioid treatment is often challenged by many 12-Step groups. Furthermore, many patients have better treatment outcomes with formal therapy in either individual or group settings.

The ability to provide counseling and education within the context of office-based practice may vary considerably, depending on the type and structure of the practice. Psychiatrists, for example, may include components of cognitive-behavioral therapy or motivational enhancement therapy during psychotherapy sessions. Some medical clinics may offer patient education, which generally is provided by allied health professionals (e.g., nurses, nurse practitioners, physician assistants). A drug abuse treatment program typically includes counseling and prevention education as an integral part of the clinic program. In a stand-alone general or family practice, the opportunities for education/counseling may be more limited. As part of their training in opioid addiction treatment, physicians should obtain, at a minimum, some knowledge of the basic principles of brief intervention in case of relapse. (See appendix E.) Physicians may want to consider providing to office staff some training in brief treatment interventions and motivational interviewing; this information could also enhance the effectiveness of treatment for other medical problems. A list of trainers may be found at http://www.motivationalinterview.org.

Many physicians already have the capability to assess and link substance abuse patients to ancillary services for substance abuse. Physicians considering making buprenorphine available to their patients should ensure that they are capable of providing psychosocial services, either in their own practices or through referrals to reputable behavioral health practitioners in their communities. In fact, the Drug Addiction Treatment Act of 2000 (DATA 2000) stipulates that, when physicians submit notification to the Substance Abuse and Mental Health Services Administration (SAMHSA) to obtain the required waiver to practice opioid addiction therapy outside the OTP setting, they must attest to their capacity to refer such patients for appropriate counseling and other non-pharmacological therapies.

It is incumbent on practitioners of buprenorphine treatment to be aware of the options and services that are available in their communities and to be able to make appropriate referrals. Physicians should be able to determine the intensity of services needed by individual patients and when those needs exceed what the practitioner can offer. Contingency plans should be established for patients who do not follow through with referrals to psychosocial treatments. Physicians should work with qualified behavioral health practitioners to determine the intensity of services needed beyond the medical services.

Treatment Monitoring

Treatment Plan

Patients and their physicians together need to reach agreement on the goals of treatment through a treatment plan that is based on assessment of the patient. Treatment plans should include both treatment goals and the conditions under which treatment is to be discontinued. The initial plan should contain contingencies for treatment failure, such as referral to a more structured treatment modality (e.g., an OTP). For polysubstance users, it is also important for patients to set a goal of abstinence from all illicit drugs, provided that counseling to address other drug use is also available. (Abstinence from all illegal or inappropriate substances of abuse should be the goal of all patients, whether single or polysubstance users.) Treatment contracts are often employed to make explicit what is expected of patients in terms of their cooperation and involvement in addiction treatment.

> Treatment plans should include both treatment goals and the conditions under which treatment is to be discontinued.

Physicians may find the sample contract (or an adapted version) in appendix H a useful tool in working with patients in an office-based setting.

After obtaining signed patient consent (according to 42 C.F.R. Part 2), physicians should clarify assessment and treatment goals with family members. Whenever possible, significant others should be engaged in the treatment process, as their involvement is likely to have a positive effect on outcomes. Conversely, when patients refuse to involve their significant others, or when the latter refuse to become involved, positive outcomes are less likely.

Frequency of Visits

During the stabilization phase, patients receiving maintenance treatment should be seen on at least a weekly basis. Part of the purpose of the ongoing assessment is to determine whether patients are adhering to the dosing regimen and handling their medications responsibly (e.g., storing it safely, taking it as prescribed, not losing it). Once a stable buprenorphine dose is reached and toxicological samples are free of illicit opioids, the physician may determine that less frequent visits (biweekly or longer, up to 30 days) are acceptable. Visits on a monthly basis are considered a reasonable frequency for patients on stable buprenorphine doses who are making appropriate progress toward treatment objectives and in whom toxicology shows no evidence of illicit drugs. However, physicians should be sensitive to treatment barriers, such as geographical issues, travel distance to treatment, domestic issues such as child care and work obligations, as well as the cost of care.

Patients' progress in achieving treatment goals should be reviewed periodically. Various goal-attainment scales, which can be administered by a nurse or case manager, can assist in monitoring and documenting patients' progress. Measures used to evaluate maintenance treatment with buprenorphine are similar to

those used for other areas of addiction treatment:

- No illicit opioid drug use occurs and no other ongoing drug use (including problematic alcohol use) is found that might compromise patient safety (e.g., ongoing abuse of alcohol and/or benzodiazepines).
- Toxicity is absent.
- Medical adverse effects are absent.
- Behavioral adverse effects are absent.
- Patient is handling the medication responsibly.
- Patient is adhering to all elements of the treatment plan (e.g., seeing a psychotherapist or attending groups as scheduled, participating in recovery-oriented activities).

Unstable Patients

Given these evaluations, physicians need to decide when they cannot appropriately provide further management for particular patients. For example, if a patient is abusing other drugs that a physician does not feel competent to manage, or if toxicology tests are still not free of illicit drugs after 8 weeks, then the physician may want to assess (1) whether to continue to treat that patient without additional evidence of ongoing counseling or (2) whether to refer the patient to specialists or to a more intensive treatment environment. Decisions should be based on the treatment plan to which the patient previously agreed.

Toxicology Testing for Drugs of Abuse

During opioid addiction treatment with buprenorphine, toxicology tests for all relevant illicit drugs should be administered at least monthly. Urine screening is the most common testing method, although testing can be performed on a number of other bodily fluids and tissues—including blood, saliva, sweat, and hair. A comprehensive discussion of urine drug testing in the primary care setting can be found in *Urine Drug Testing in Primary Care: Dispelling the Myths & Designing Strategies* (Gourlay et al. 2002).

Methadone and heroin metabolites are each detected by commercially available urine-testing kits. Buprenorphine does not cross-react with the detection procedures for methadone or other opioids; therefore, it will not be detected in a routine urine drug screen. Both physicians and patients should be aware of this fact.

Buprenorphine and its metabolites are excreted in urine. Urine testing for buprenorphine can be performed at a medical laboratory, but at the time of this document's publication, there are no CLIA-waived, in-office buprenorphine urine test kits commercially available.

There are two primary reasons to consider testing for buprenorphine: (1) in new patients to confirm that they do not already have buprenorphine in their system, (2) to assist with evaluating adherence in patients on buprenorphine treatment. (Refer to chapter 3 for additional information on drug-testing methodologies.) As new testing procedures and protocols are recommended for use in addiction treatment with buprenorphine, SAMHSA will be making additional information available through the Division of Pharmacologic Therapies (DPT) Web site at http://www.dpt.samhsa.gov/.

Discontinuation of Medication

Under ideal conditions, discontinuation of medication should occur when a patient has achieved the maximum benefit from treatment and no longer requires continued treatment to maintain a drug-free lifestyle. Once this goal is achieved, buprenorphine should be tapered slowly and appropriately while psychosocial services continue to be provided. Patients should be assessed for continued stability in maintaining their drug-free lifestyle. Patients should then be followed with psychosocial services and/or the reintroduction of medication, if needed, for continued progress.

Certain situations undoubtedly will arise, however, in which a physician may feel that a patient is not progressing satisfactorily. For example, a patient may not be in compliance with the treatment plan or with office procedures (e.g., timely payment). Under some conditions, physicians may consider involuntary termination of treatment, but must be careful to not abandon patients. Physicians can and should take a variety of actions to prevent this situation. Physicians should have written policies in place regarding patient behavior, office procedures, and adherence to treatment. These policies should be discussed with patients before initiating buprenorphine treatment, and patients should agree to comply with these policies.

Physicians should develop practices for dealing with minor infractions of rules or policies and with minor nonadherence to treatment plans. Clearly defined points should be identified at which patients will be notified that they are not adhering to treatment plans, and they should be given the opportunity to improve in this regard. In the event of involuntary termination of treatment, it is necessary for physicians to make appropriate referrals—to OTPs, to other physicians who are willing to prescribe buprenorphine, or to other appropriate treatment facilities. If a patient will not be receiving OAT in another treatment setting, the physician must manage the appropriate withdrawal of buprenorphine so as to minimize withdrawal discomfort. A patient may or may not be willing to accept referrals made on his or her behalf, but physicians must make good faith efforts to ensure that their patients have an appropriate level of care available after their own therapeutic involvement is ended.

For more information about treatment management issues, see the forthcoming TIP *Medication-Assisted Treatment for Opioid Addiction* (CSAT in development). The treatment management principles addressed in that TIP will also be applicable to office-based buprenorphine treatment.

5 Special Populations

In This Chapter...

Patients With Medical Comorbidities

Pregnant Women and Neonates

Adolescents/ Young Adults

Geriatric Patients

Patients With Significant Psychiatric Comorbidity

Polysubstance Abuse

Patients With Pain

Patients Recently Discharged From Controlled Environments

Healthcare Professionals Who Are Addicted to Opioids

Overview

The presence of certain life circumstances or comorbid medical or psychosocial conditions warrant special attention during the evaluation and treatment of opioid addiction with buprenorphine. Patients with circumstances or conditions that require special attention include those with certain medical comorbidities (e.g., AIDS, tuberculosis), concurrent mental disorders, or concurrent alcohol or other substance abuse disorders, as well as pregnant women, adolescents, geriatric patients, patients under the jurisdiction of the criminal justice system, and healthcare professionals who are addicted. Because of the unique issues presented by these circumstances, addiction treatment for these patients may require additional training or specialty care and consultation. Before treating individuals with these circumstances for opioid addiction in an office setting, physicians should consider whether patient needs can be met with the resources at hand or if referral to specialized treatment programs or to addiction specialists is indicated.

Patients With Medical Comorbidities

Patients addicted to opioids who present for treatment often have other comorbid medical problems. These conditions are often a consequence of high-risk behaviors, including injection drug use (intravenous, intramuscular, or subcutaneous), or of the direct toxic effects of the active and inert ingredients in illicit drugs. The prevalence of infectious diseases (e.g., HIV/AIDS, hepatitis B and C, tuberculosis, skin and soft tissue infections, syphilis and other sexually transmitted diseases [STDs]) is increased in these patients and should be screened for, as outlined in chapter 3. Other comorbid conditions (e.g., seizure disorders, valvular heart disease secondary to endocarditis, pulmonary hypertension secondary to talc granulomatosis, lymphedema, pseudoaneurysms of the neck and groin secondary to

thrombophlebitis, and renal insufficiency secondary to heroin-associated nephropathy) also are seen in this population and may require special attention. Patients with a history of endocarditis need antibiotic prophylaxis before certain dental procedures. Patients with a history of hepatitis C may require hepatitis A and B vaccinations and may be intolerant of potentially hepatotoxic medications. One retrospective study found that liver function tests were significantly elevated in patients treated with buprenorphine who also had a history of hepatitis, suggesting that liver function tests should be monitored in these patients on a regular basis during buprenorphine treatment (Petry et al. 2000). A detailed discussion of medical comorbidities in addiction is beyond the scope of this chapter and is reviewed extensively elsewhere (Cherubin and Sapira 1993; Stein 1990).

Treatment of opioid addiction in patients with comorbid medical conditions is likely to result in better outcomes for the comorbid conditions than would be achieved in the absence of treatment of the substance use disorder. Moatti et al. (2000) found that patients on buprenorphine tended to be more compliant with highly active antiretroviral therapies (HAART) than patients who were not treated concurrently for opioid addiction.

Pharmacological treatments of comorbid medical disorders may have important drug interactions with buprenorphine due to shared pharmacokinetic properties. Although Carrieri et al. (2000) found no detrimental short-term effect of buprenorphine treatment on the effect of HAART on viral load, buprenorphine is metabolized by the hepatic cytochrome P450 3A4 enzyme system and will likely interact with other medications metabolized by the same system. Certain antiretrovirals may occupy the cytochrome P450 3A4 system and thus inhibit the metabolism of buprenorphine. Other drugs that induce the cytochrome P450 3A4 system (e.g., certain antituberculosis, anticonvulsant, and antiretroviral medications) may decrease serum concentrations of buprenorphine, resulting in opioid withdrawal or decreased effectiveness. Because the interactions of most medications with buprenorphine have not been systematically studied, physicians should monitor for any signs or symptoms of opioid side effects, loss of effectiveness, or withdrawal after a patient starts any new medications. Buprenorphine dose adjustments may be necessary after starting new medications, even for patients who have been on a stable maintenance dose.

Other potential, and as yet unknown, drug interactions include the possibility of buprenorphine increasing or decreasing metabolism of medications used in treating comorbid medical conditions. Informing patients of potential drug–drug interactions, especially sedation or precipitated opioid withdrawal, is important to prevent jeopardizing adherence with medical treatment and/or precipitating relapse to illicit opioid use.

In summary, it is important to screen for and manage common comorbid medical conditions in patients being treated with buprenorphine for opioid addiction and to anticipate known and potential drug interactions. For additional information on drug–drug interactions with buprenorphine, refer to chapter 2.

Pregnant Women and Neonates

The continued use of heroin during pregnancy, with its attendant risks of infection, overdose, and intrauterine withdrawal, is life threatening to both the woman and the fetus. Research on the safety and efficacy of buprenorphine in pregnant women and neonates is scarce, however. If a patient is pregnant or is likely to become pregnant during the course of opioid addiction treatment, the physician must consider whether buprenorphine is an appropriate option for treatment. Physicians should weigh all the risks and benefits of treatment with buprenorphine against all the risks associated with the continued use of illicit opioids. Methadone is currently the standard of care in the United States for the treatment of opioid addiction in pregnant

women. Methadone has been shown to be safe and effective for both pregnant women and neonates.

The FDA classifies buprenorphine as a Pregnancy Category C drug. The FDA Pregnancy Labeling Task Force, whose long-term goal is to determine how animal toxicologic information contributes to clinically meaningful information in pregnancy, assigns a human prescription drug to Pregnancy Category C (1) if animal reproduction studies have shown an adverse effect on the fetus, (2) if there are no adequate and well-controlled studies in humans, and (3) if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. In addition to considering the FDA warnings pertaining to the use of buprenorphine in pregnant women, physicians also must consider the risks of infectious diseases and lifestyle issues (e.g., poor nutrition, lack of prenatal care) when addressing the needs of these patients.

Effects of Buprenorphine in Pregnancy

Data on the pharmacokinetics of buprenorphine in pregnant women and neonates are extremely limited (Johnson et al. 2003*a*; Marquet et al. 1997). Likewise, data are limited regarding the clinical use of buprenorphine for the maintenance treatment of opioid addiction in pregnant women. The literature in this area generally consists of case reports and a small number of prospective studies; there have been no controlled clinical trials. In case reports from European and Australian sources on the use of buprenorphine in opioid-addicted pregnant women, doses have ranged from 0.4 to 24 mg per day. In these limited reports, pregnancies have generally progressed normally, with low rates of prematurity or other problems. Maternal clinical laboratory data in these reports generally have been within normal limits; or were deemed either clinically nonsignificant at levels expected during pregnancy, when outside normal limits, or were due to factors other than the medication. For a complete review of the published literature on the use of buprenorphine in the treatment of opioid addiction in pregnant women, see Johnson et al. 2003*a*.

Infants of Mothers Treated With Buprenorphine

Buprenorphine and its metabolite norbuprenorphine have been found in high concentrations in the blood, urine, and meconium of the neonates of women maintained on buprenorphine (Johnson et al. 2003*a*; Marquet et al. 1997).

The published literature includes information on at least 309 infants born to women maintained on buprenorphine treatment. Although not systematically studied, a neonatal abstinence syndrome (NAS) has been reported in 191 of these 309 infants, with approximately one-half of those with NAS requiring treatment. In more than 40 percent of the cases, however, evaluation of the abstinence syndrome was confounded by other drug use by the mothers. Overall, although no randomized controlled trials have been reported, the NAS associated with buprenorphine has been reported to be less intense than that observed with methadone.

> Methadone is currently the standard of care in the United States for the treatment of opioid addiction in pregnant women.

One prospective open-label study (Fischer et al. 2000) found signs of NAS in 7 of 15 neonates exposed to buprenorphine in utero. Of these 15 neonates, 3 had moderate signs of NAS that required treatment, 4 had mild signs of NAS that required no treatment, and 8 had no signs of NAS. A second prospective open-label study (Johnson et al. 2003*a*)

reported NAS in 3 of 3 neonates; however, none required treatment with medications.

NAS from buprenorphine generally appears within the first 2 days of life, peaks within 3 or 4 days, and lasts for 5 to 7 days. Few infants were reported to have had a withdrawal syndrome for 6 to 10 weeks.

Similar to the treatment of NAS following exposure to methadone, several different medications (including chlorpromazine, phenobarbital, benzodiazepine, paregoric elixir, and morphine drops) have been used successfully to treat the NAS associated with buprenorphine. The American Academy of Pediatrics recommends tincture of opium as the medication of choice for treatment of neonatal opioid withdrawal symptoms (American Academy of Pediatrics Committee on Drugs 1998).

Breast Feeding While on Buprenorphine Treatment

The limited human pharmacokinetic data show that buprenorphine passes into the breast milk of lactating women at a plasma-to-milk ratio of approximately 1. As a result, and because of the poor oral bioavailability of buprenorphine, the nursing infant will be exposed to only 1/5–1/10 of the total amount of buprenorphine available.

The literature includes reports on approximately 40 to 50 women who were maintained on buprenorphine and who breastfed after delivery (Johnson et al. 2003*a*; Lejeune et al. 2001; Loustauneau et al. 2002; Marquet et al. 1997). These reports indicate that buprenorphine present in breast milk does not appear to suppress NAS. Additionally, NAS has not been observed after the cessation of breastfeeding by women who were maintained on buprenorphine (Loustauneau et al. 2002).

Although the Subutex® and Suboxone® package inserts state that breastfeeding is not advised in mothers treated with these medications, it is the consensus of the panel that any effects of these medications on the breastfed infant would be minimal and that breastfeeding is not contraindicated. However, given the limited literature in this subject area, physicians are advised to use their professional judgment in their recommendations.

The Buprenorphine/Naloxone Combination in Pregnancy

The panel notes that there is a question whether the buprenorphine/naloxone combination is or is not recommended for use in pregnancy. Naloxone is labeled by FDA as a Pregnancy Category B drug. The FDA Pregnancy Labeling Task Force assigns a human prescription drug to Pregnancy Category B (1) if animal reproduction studies have failed to demonstrate a risk to the fetus and (2) if there are no adequate and well-controlled studies in pregnant women. Despite the fact that naloxone is classified as a Pregnancy Category B drug, it should be used with caution in pregnant women who are addicted to opioids. Because both mother and fetus will be dependent on the opioids used by the mother, administration of naloxone could precipitate withdrawal in both.

If it is determined that buprenorphine is the only acceptable option for the treatment of a pregnant woman, and she understands the issues and risks, then she should be treated with buprenorphine monotherapy so as not to risk fetal exposure to naloxone. It should be noted that use of buprenorphine monotherapy, because of its greater potential for abuse, necessitates more frequent monitoring of patients and of their medication supplies. To prevent abuse and diversion of the buprenorphine monotherapy formulation, quantities of take-home supplies and quantities provided via prescription should be smaller compared to treatment with the buprenorphine/naloxone combination formulation.

Summary

Buprenorphine is classified by FDA as a Pregnancy Category C drug. Data from controlled studies on the use of buprenorphine in pregnant women are needed. The available evidence does not show any causal adverse effects on pregnancy or neonatal outcomes from buprenorphine treatment, but this evidence is from case series not from controlled studies. Methadone is currently the standard of care in the United States for the treatment of heroin addiction in pregnant women. Pregnant women presenting for treatment of opioid addiction should be referred to specialized services in methadone maintenance treatment programs. If such specialized services are refused by a patient or are unavailable in the community, maintenance treatment with the buprenorphine monotherapy formulation may be considered as an alternative. In such circumstances, it should be clearly documented in the medical record that the patient has refused methadone maintenance treatment, or that such services were unavailable; that she was informed of the risks of using buprenorphine, a medication that has not been thoroughly studied in pregnancy; and that she understands those risks.

Adolescents/Young Adults

The use of buprenorphine for the treatment of opioid addiction in adolescents has not been systematically studied. It is known, however, that patients younger than 18 years of age, with relatively short addiction histories, are at particularly high risk for serious complications of addiction (e.g., overdose deaths, suicide, HIV, other infectious diseases). Many experts in the field of opioid addiction treatment believe that buprenorphine should be the treatment of choice for adolescent patients with short addiction histories. Additionally, buprenorphine may be an appropriate treatment option for adolescent patients who have histories of opioid abuse and addiction and multiple relapses but who are not currently dependent on opioids. Buprenorphine may be preferred to methadone for the treatment of opioid addiction in adolescents because of the relative ease of withdrawal from buprenorphine treatment. Because adolescents often present with short histories of drug use, detoxification with buprenorphine, followed by drug-free or naltrexone treatment, should be attempted first before proceeding to opioid maintenance. Naltrexone may be a valuable therapeutic adjunct after detoxification. Naltrexone has no abuse potential and may help to prevent relapse by blocking the effects of opioids if the patient relapses to opioid use. Naltrexone has been a valuable therapeutic adjunct in some opioid-abusing populations, particularly youth and other opioid users early in the course of addiction. Naltrexone is most likely to be effective for patients with strong support systems that include one or more individuals willing to observe, supervise, or administer the naltrexone on a daily basis. In those adolescent patients in whom detoxification is followed by relapse, buprenorphine maintenance may then be the appropriate alternative. Refer to chapter 4 for buprenorphine maintenance and detoxification procedures.

> Buprenorphine can be a useful option for the treatment of adolescents who have opioid addiction problems.

The treatment of patients younger than 18 years of age can be complicated due to psychosocial considerations, the involvement of family members, and State laws concerning consent and reporting requirements for minors. Ancillary counseling and social services are important to support cooperation and follow through with the treatment regimen.

Parental Consent

Parental consent is a critical issue for physicians who treat adolescents addicted to opioids. In general, adult patients with "decisional capacity" have the unquestioned right to decide which treatments they will accept or refuse, even if refusal might result in death. The situation for adolescents is somewhat different, however. Adolescents do not have the legal status of adults unless they are legally "emancipated minors." Adolescents' rights to consent to or to refuse medical treatment differ from those of adults. Rules differ from State to State regarding whether an adolescent may obtain substance use disorder treatment without parental consent. Some State statutes governing consent and parental notification specify consideration of a number of fact-based variables, including the adolescent's age and stage of cognitive, emotional, and social development, as well as issues concerning payment for treatment and rules for emancipated minors.

More than one-half of the States permit individuals younger than 18 years of age to consent to substance use disorder treatment without parental consent. In States that do require parental consent, providers may admit adolescents to treatment when parental consent is obtained. In States requiring parental notification, treatment may be provided to an adolescent when the adolescent is willing to have the program communicate with a parent. Histories of neglect or abuse may be revealed during the care of adolescent patients, and physicians must be aware of reporting requirements in their State. Mandatory child abuse reporting takes precedence over Federal addiction treatment confidentiality regulations, according to Title 42, Part 2 of the Code of Federal Relations (42 C.F.R. Part 2).

Additional difficulties may arise when adolescents requesting treatment refuse to permit notification of a parent or guardian. With one very limited exception, the Federal confidentiality regulations prohibit physicians (or their designees) from communicating substance abuse treatment information to any third parties, including parents, without patient consent. The sole exception allows a "program director" (i.e., treating physician) to communicate "facts relevant to reducing a threat to the life or physical well-being of the applicant or any other individual to the minor's parent, guardian, or other person authorized under State law to act in the minor's behalf," when the program director believes that the adolescent, because of extreme youth or mental or physical condition, lacks the capacity to decide rationally whether to consent to the notification of his or her parent or guardian (42 C.F.R. Part 2, Subpart B, Section 2.14d 2001). The program director must believe the disclosure to a parent or guardian is necessary to cope with a substantial threat to the life or physical well-being of the adolescent applicant or someone else. In some cases, communication with State child protection agencies or judicial authorities may be an acceptable alternative, or the required course of action, if the physician believes neglect or abuse has already occurred.

Treatment Setting

The more intensive a proposed treatment is, the more risk a program assumes in admitting adolescents without parental consent. Outpatient programs may have a better justification for admitting adolescents without parental consent than do intensive outpatient or residential programs.

Summary

Buprenorphine can be a useful option for the treatment of adolescents who have opioid addiction problems. The treatment of addiction in adolescents is complicated by a number of medical, legal, and ethical considerations, however. Physicians intending to treat addiction in adolescents should be thoroughly familiar with the laws in their State regarding parental consent. Physicians who do not specialize in the treatment of opioid addiction or adolescent medicine should strongly consider consulting with, or referring adolescent

addiction patients to, such specialists. Additionally, State child protection agencies can be a valuable resource when determining the proper disposition for adolescent patients.

Geriatric Patients

Literature on the use of buprenorphine in geriatric patients is extremely limited. Because of potential differences in rates of metabolism and absorption compared to the nonelderly, care should be exercised in the use of buprenorphine in elderly individuals. Particular care should be exercised during buprenorphine induction both because of differences in body composition and because of the possibility of medication interactions.

Patients With Significant Psychiatric Comorbidity

The association of psychopathology and opioid addiction is well established. Psychiatric symptoms and disorders may be drug-induced, independent, or interrelated. Substance use and addiction can mimic, exacerbate, or precipitate psychiatric symptoms and disorders. Most substances of abuse produce moderate-to-severe psychiatric symptoms, and there is a complex association between substance use and psychiatric status.

A study of rates of psychiatric disorders among 716 patients addicted to opioids seeking treatment with methadone (Brooner et al. 1997), found a lifetime rate of 47 percent, and a current rate of 39 percent. Of note, patients in this study were stabilized in treatment for 1 month before the psychiatric evaluation. Other, earlier studies have reported higher rates of depression, antisocial personality characteristics, schizophrenia or schizotypal features, manic symptomatology, and alcoholism in opioid-addicted patients. For example, in a study of 533 opioid-addicted patients in treatment for their drug problems, Rounsaville and colleagues (1982) found that 86.9 percent met diagnostic criteria for some psychiatric disorder (including personality disorders) in their lifetimes, and 70.3 percent met criteria for a current psychiatric disorder. It should be noted, however, that, although the rates of major depressive disorder, alcoholism, antisocial personality, minor mood disorders, and anxiety disorders in this group exceeded those found in the general population, the rates of schizophrenia and mania did not.

Although the etiological significance of psychiatric disorders in the genesis of opioid addiction is not established, it is known that treatment for both conditions is necessary for substance abuse treatment to be effective. Therefore, the presence and severity of comorbid psychiatric conditions must be assessed in patients who are opioid addicted before, or while, initiating buprenorphine treatment, and a determination must be made whether referral to specialized behavioral health services is indicated.

Assessment is critical to determine whether psychiatric symptoms represent primary psychiatric disorders or substance-induced conditions.

Untreated or inadequately treated psychiatric disorders can interfere with the effective treatment of addiction. Polysubstance use and psychiatric problems are both associated with negative treatment outcomes unless they are identified and treated appropriately. For example, patients with major depression or dysthymia are more likely to use illicit drugs during treatment than patients who do not suffer from depression. Assessment is critical to determine whether psychiatric symptoms represent primary psychiatric disorders or substance-induced conditions. Primary

psychiatric disorders may improve but do not dissipate with abstinence or maintenance therapies, and these disorders may require additional treatment. The psychiatric disorders most commonly encountered in patients who are opioid addicted are other substance abuse disorders, depressive disorders, posttraumatic stress disorder, substance-induced psychiatric disorders, and antisocial and borderline personality disorders.

The presence of comorbid psychiatric disorders should not exclude patients from admission to opioid addiction treatment. Diagnosis of psychiatric disorders is critical to matching patients to appropriate treatment services. In first encounters with patients, it is essential to evaluate for the presence of suicidal or homicidal ideations, signs or symptoms of acute psychosis, and other acute or chronic psychiatric problems that may render patients unstable. Initiation of antidepressant therapy, in conjunction with treatment for opioid addiction, may be considered in patients presenting with signs or symptoms of depression. If manic behavior is present, attempts should be made to determine whether it is substance induced or whether the etiology is a primary mood disorder.

When psychiatric symptoms are severe or unstable, hospitalization for protection and containment may be appropriate to ensure the safety of the patient and others. Patients who are considered actively suicidal should not receive buprenorphine on an outpatient, prescription basis. Rather, they should be referred immediately for appropriate treatment, which may include psychiatric hospitalization. Those who are not currently suicidal but who have a history of suicidal ideation or attempts should be monitored closely in terms of medication supply and followup.

Psychiatrically stable patients can be readily accepted into treatment and stabilized on buprenorphine; subsequently they may receive additional psychiatric assessment to identify conditions requiring treatment. Patients who present with depression during the maintenance phase of buprenorphine treatment require continued assessment and should be treated appropriately.

Polysubstance Abuse

The abuse of multiple drugs (polysubstance abuse) among individuals addicted to opioids is common. Although polysubstance abuse or dependence may be identified during assessment, physicians should remain alert to their presence throughout the course of addiction treatment.

Pharmacotherapy with buprenorphine for opioid addiction will not necessarily have a beneficial effect on an individual's use of other drugs. It is essential that patients be referred for treatment of addiction to other types of drugs when indicated. In addition, care must be exercised in the prescribing of buprenorphine for patients who abuse alcohol and for those who abuse sedative/hypnotic drugs (especially benzodiazapines) because of the documented potential for fatal interactions. (See chapter 2 for further information.)

Patients With Pain

Patients Being Treated for Pain Who Become Dependent on Opioids

Patients who need treatment for pain *but not for addiction* should be treated within the context of their regular medical or surgical setting. They should not be transferred to an opioid maintenance treatment program simply because they are being prescribed opioids and have become physically dependent on the opioids in the course of their medical treatment.

It can be difficult to distinguish between the legitimate desire to use opioids for pain relief and the desire to procure them for purposes of obtaining a high. This may be especially true in patients who have become physically dependent on opioids in the course of the treatment of a pain condition when that pain has been undertreated and inadequately

relieved. Figure 5–1 presents some distinguishing features in the use of opioids by patients who are not addicted and who are using opioids for pain relief versus their use by patients who are addicted.

Patients Who Are Addicted to Opioids and Who Require Treatment for Pain

Behaviors associated with drug abuse frequently result in the development of acute and chronic pain conditions. These conditions may be caused by the toxic effects of the drug itself, as well as by trauma and infection. Patients receiving addiction treatment also may experience pain due to illness or injury unrelated to drug use. Physicians must manage this pain efficiently and appropriately. Opioids are among the most effective available options for managing pain, but they are often not prescribed to patients receiving treatment for addiction out of fear of "feeding the addiction" or of triggering relapse in currently abstinent patients. State laws governing the prescription of opioids to known substance abusers may place prescribing physicians at risk for prosecution unless the medical record clearly distinguishes between treatment of the addiction and treatment of the pain condition.

Treatment Approach. Little clinical experience is documented regarding the treatment of pain in patients receiving buprenorphine. Pain in patients receiving buprenorphine treatment initially should be treated with nonopioid analgesics when appropriate. Although buprenorphine itself has powerful analgesic properties, the once-daily administration of buprenorphine, as used for the treatment of opioid addiction, often does not provide sufficiently sustained relief of pain. Additionally, the onset of action of analgesia with buprenorphine may not be adequate for the treatment of acute pain. In a study of the use of buprenorphine for acute analgesia (Nikoda et al. 1998), the high analgesic activity of buprenorphine was comparable to that of morphine, but the onset of action was found to be inadequate for urgent care.

Patients maintained on buprenorphine whose acute pain is not relieved by nonopioid

Figure 5–1

Clinical Features Distinguishing Opioid Use in Patients With Pain Versus Patients Who Are Addicted to Opioids

Clinical Features	Patients With Pain	Patients Who Are Addicted to Opioids
Compulsive drug use	Rare	Common
Crave drug (when not in pain)	Rare	Common
Obtain or purchase drugs from nonmedical sources	Rare	Common
Procure drugs through illegal activities	Absent	Common
Escalate opioid dose without medical instruction	Rare	Common
Supplement with other opioid drugs	Unusual	Frequent
Demand specific opioid agent	Rare	Common
Can stop use when effective alternate treatments are available	Usually	Usually not
Prefer specific routes of administration	No	Yes
Can regulate use according to supply	Yes	No

medications should receive the usual aggressive pain management, which may include the use of short-acting opioid pain relievers. While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. Note that, until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids in patients who have been maintained on buprenorphine, and higher doses of short-acting opioids may be required. Non-combination opioid analgesics are generally preferred to avoid the risk of acetaminophen or salycilate toxicity when combination products are used at the doses that are likely to be required for pain control in patients who have been maintained on buprenorphine. Analgesic dose requirements should be expected to decrease as buprenorphine clears the body.

…it may be difficult to achieve analgesia with short-acting opioids in patients who have been maintained on buprenorphine…

When restarting buprenorphine administration, physicians should refer to chapter 4 for induction procedures. To prevent the precipitation of withdrawal, buprenorphine should not be restarted until an appropriate period after the last dose of the opioid analgesic, depending on the half-life of the opioid analgesic used.

Patients who are receiving opioids for chronic severe pain may not be good candidates for buprenorphine treatment because of the ceiling effect on buprenorphine's analgesic properties. This rationale also would be applicable to terminally ill patients. In patients who are maintained on buprenorphine and require end-of-life opioid analgesia, buprenorphine administration should be discontinued, unless the buprenorphine provides adequate analgesia or the patient prefers buprenorphine for some other reason.

In patients who are opioid addicted and who have severe chronic pain, methadone several times per day or other "round the clock" (rather than as required) long-acting, full-agonist medications may be the best alternative for treatment. This form of treatment is often best undertaken in conjunction with an Opioid Treatment Program (OTP). However, if the physician is (1) otherwise qualified to treat the condition causing the pain and (2) careful to document that the primary purpose of the opioid pharmacotherapy is the management of that pain condition, then it may be acceptable to treat that patient in the office setting without further referral. As long as this type of patient remains compliant and is not abusing the pain medication or other drugs, there is no legal need for the patient to be treated in an OTP or with buprenorphine for the preexisting or concurrent addictive disorder. However, the Drug Enforcement Administration (DEA) frowns on the use of this as a rationale to treat the "pain of withdrawal" or spurious and ill-defined pain conditions to justify unsanctioned opioid maintenance. Patients who are on chronic opioids for pain management and who have a history of drug abuse or addiction can be referred to a 12-Step program or other self-help group to help them maintain their level of recovery. Random drug screening also can reassure the physician that both physician and patient are staying within lawful bounds.

Because all pharmacological treatment with opioids is highly regulated, physicians who desire to use opioids to treat chronic pain in patients who are at risk for opioid addiction or relapse are advised to consult with a colleague knowledgeable in opioid maintenance pharmacology.

Patients Recently Discharged From Controlled Environments

This section focuses on the assessment and treatment of patients with opioid addiction who are recently released from controlled environments (e.g., prison) and who would be presumed to have involuntarily detoxified from opioids while incarcerated. Other situations that may warrant special consideration include (1) patients discharged from extended hospital or rehabilitation center stays, (2) patients returning from extended overseas travel/expatriate duty in countries without easy access to licit or illicit opioids, and (3) other conceivable situations that may have caused an involuntary break in active use of and addiction to opioids.

The findings on patient assessment will help to clarify the diagnosis of opioid dependence/addiction and whether a patient is at serious risk for resumption of an addiction lifestyle if not treated with a buprenorphine maintenance regimen. Other considerations for providers include possible psychosocial needs and issues, as well as collateral contacts that may be required when treating patients who may have continuing involvement with the criminal justice system.

Opioid Addiction in Patients Under the Jurisdictions of Criminal Justice Systems

It is well documented that the crimes committed by most of the more than 1 million individuals incarcerated in the United States are related to the abuse of or addiction to drugs. Opioids are the preferred contraband drugs of choice in prisons and can be relatively easy to obtain in some institutions. Prison environments and inmate culture reinforce the addiction cycle and addiction lifestyle. Recidivism rates are higher in patients with a history of opioid addiction because they are typically reincarcerated after failing parole or drug-testing requirements.

Assessment of Patients Who Are Opioid Addicted and Who Are Recently Released From Controlled Environments

Physicians should consider the following factors when assessing for addiction in patients recently released from controlled environments: length of incarceration; postrelease addiction patterns and cycles; addiction treatment history (drug-free, outpatient, recovery, or therapeutic community); self-help involvement (before, during, and since incarceration); and reported triggers of illegal drug use and addiction upon release. Physicians should evaluate for the presence of comorbid mental health issues or history of other drug or alcohol use that could complicate buprenorphine treatment. (See chapter 3 for further information.) If office-based buprenorphine treatment is being considered, physicians should carefully assess the patient's level of commitment to treatment and the likelihood of self control.

Assessing Psychosocial Issues

Attention to psychosocial issues is important in patients who are coming out of controlled environments. Issues that often affect the success of addiction treatment include

- Number and/or length of incarcerations
- Types of crimes committed (e.g., violent offenses, drug-related)
- Gang affiliations
- Type and length of parole or probation (e.g., whether the patient will be given regular or random drug testing)
- The patient's collateral contacts and reporting requirements

- Prior and current involvement of the patient's social support system (e.g., the presence of opioid addiction problems or current use in family members)
- Recent changes in familial or marital relationships
- Whether permission from the criminal justice system is required for treatment with buprenorphine

Physicians should ask the patient whether he or she has a reasonable plan for a stable lifestyle (e.g., involvement in job, school, family) and whether the plan includes total abstinence from drug and alcohol use. If there is no plan, the physician should ask why not and offer to help the patient create one.

Final determination of a patient's appropriateness for buprenorphine treatment will involve analysis of the subjective assessment and disclosed information, as well as a review of medical records to determine treatment compliance and cooperation. Physicians should assess a patient's psychosocial needs and the compatibility of the patient with the potential limitations of an outpatient, office-based environment.

Determining Appropriateness for Buprenorphine Treatment

A number of issues should be considered in determining the most appropriate treatment modality for patients with addiction who are recently released from controlled environments. If a methadone clinic alternative is available, the physician should determine the factors that may preclude referral. The existing doctor/patient relationship should be assessed, as well as eligibility for other assistance, and the presence of a solid support system. A physician's limitations with regard to potentially intensive buprenorphine monitoring activities should be considered, as a treating physician may be called on to determine, verify, and explain a treatment regimen (e.g., to parole and probation officers); to document the patient's compliance; and to interact with the legal system, employers, and others. Physicians should consider potential issues associated with detoxification in jail if a patient is reincarcerated. The cost of treatment needs to be considered, as well as whether the costs are covered by a patient's health insurance. Additionally, potential risk issues need to be considered (e.g., diversion, overdose, criminal activity while in a limited, professional care setting, mixing with other patients).

Healthcare Professionals Who Are Addicted to Opioids

A substantial problem of addiction to prescription opioids exists among physicians and other health professionals, especially within certain specialties (e.g., anesthesiology) (Talbott et al. 1987). Prescription opioid addiction in health professionals should be viewed as an occupational hazard of the practice of medicine. Health professionals who have substance abuse disorders often require specialized, extended care.

If the addictive drug of choice is present in the workplace, reentry planning after initial treatment should consider relapse by the health professional who is in early recovery. The opioid antagonist naltrexone and other adjunctive medications are often required. Naltrexone has been a routine adjunct for the treatment of anesthesiologists who are addicted to opioids. The key to successful naltrexone use by a highly motivated patient is a strong social support system that includes a significant other, coworker, or health professional who directly observes the naltrexone use on a regular basis.

Buprenorphine may be an appropriate treatment option for some health professionals who are opioid dependent, but the use of a partial agonist would need to be part of a comprehensive, monitored recovery plan. If the professional has already come under regulatory scrutiny, such a plan might require approval by the State authority to which the professional reports.

6 Policies and Procedures

In This Chapter...

The DATA 2000 Waiver

Preparing for Office-Based Opioid Treatment

Confidentiality and Privacy

Buprenorphine Use in OTPs

Overview

This chapter discusses policies and procedures relating to the Drug Addiction Treatment Act of 2000 (DATA 2000), to preparations for providing opioid addiction treatment in practices that are new to this form of care, to State and Federal laws and regulations that protect the privacy and confidentiality of addiction treatment information, and to the use of buprenorphine in federally regulated Opioid Treatment Programs (OTPs). Physicians should become thoroughly familiar with these issues before engaging in the practice of opioid addiction treatment (Brooks 1997). In addition, readers are referred to appendix F, which contains additional information about many of these topics.

The DATA 2000 Waiver

DATA 2000 enables *qualifying physicians* to receive a *waiver* from the special registration requirements in the Narcotic Addict Treatment Act (NATA) of 1974 (and its enabling regulations, including Title 42, Part 8 of the Code of Federal Regulations, that govern OTPs) for the provision of opioid addiction treatment. This waiver allows qualifying physicians (see "Physician Waiver Qualifications") to *prescribe or dispense* Schedule III, IV, and V "narcotic" medications for the treatment of opioid addiction in the office and other clinical settings if (and only if) those medications have been approved by the Food and Drug Administration (FDA) for use in addiction treatment. As of this writing, Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone) sublingual tablets are the only Schedule III, IV, or V pharmaceuticals to have received such FDA approval. NATA makes it illegal for narcotics to be used "off label" to treat opioid addiction. This prohibition extends even to other forms of buprenorphine (e.g., Buprenex®) that have not been specifically approved for the treatment of opioid addiction.

Notification of Intent

To receive a DATA 2000 waiver to practice opioid addiction treatment with approved Schedule III, IV, and V opioid medications, a physician must notify the Substance Abuse and Mental Health Services Administration (SAMHSA) of his or her intent to begin dispensing or prescribing this treatment. This Notification of Intent must be submitted to SAMHSA before the initial dispensing or prescribing of opioid treatment. Notification of Intent forms can be obtained on the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov. Forms can be submitted to SAMHSA online or printed out and then submitted via ground mail or fax.

The Notification of Intent must contain information on the physician's qualifying credentials (as defined below) and additional certifications, including that the physician has the capacity to refer addiction patients for appropriate counseling and other nonpharmacological therapies, and that the physician will not have more than 30 patients on such addiction treatment at any one time. (Note that the 30-patient limit applies both to physicians in solo practice and to entire group practices, and the limit is not affected by the number of locations of practice of the physicians or groups.)

Physicians who meet the qualifications defined in DATA 2000 are issued a waiver by SAMHSA and a special identification number by the Drug Enforcement Administration (DEA). DEA has issued regulations that require physicians to include this identification number on all records when dispensing and on all prescriptions when prescribing approved opioid medications (currently only Subutex® and Suboxone®) for opioid addiction.

Immediate-Type Notifications

Under DATA 2000, a physician may initiate opioid addiction treatment for "an individual patient" after submitting a Notification of Intent to SAMHSA but *before receipt of a waiver and identification number*. To provide this "immediate-type" treatment, a physician must not only submit the usual Notification of Intent to SAMHSA but also must include notification of intent to begin immediately treating an individual patient. SAMHSA's Notification of Intent form includes a checkbox for indicating this immediate-type intent.

Physician Waiver Qualifications

To qualify for a waiver under DATA 2000, a licensed physician (M.D. or D.O.) must meet any one or more of the following criteria:

- The physician holds a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
- The physician holds an addiction certification from the American Society of Addiction Medicine (ASAM).
- The physician holds a subspecialty board certification in addiction medicine from the American Osteopathic Association (AOA).
- The physician has, with respect to the treatment and management of patients who are opioid addicted, completed not less than 8 hours of training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) that is provided by ASAM, the American Academy of Addiction Psychiatry, the American Medical Association, AOA, the American Psychiatric Association, or any other organization that the Secretary of the U.S. Department of Health and Human Services (DHHS) determines is appropriate for purposes of this subclause.
- The physician has participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in Schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the DHHS Secretary by the sponsor of such approved drug.
- The physician has such other training or experience as the State medical licensing

board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage patients who are opioid addicted.

- The physician has such other training or experience as the DHHS Secretary considers as demonstrating the ability of the physician to treat and manage opioid-dependent patients. Any criteria of the DHHS Secretary under this subclause shall be established by regulation.

For More Information

Proper training on the use of buprenorphine will be key to the successful introduction of this new treatment paradigm, regardless of the clinical setting of buprenorphine treatment. Thus, SAMHSA and the consensus panel strongly encourage all physicians who plan to practice opioid addiction treatment with buprenorphine to participate in a DATA 2000-qualifying 8-hour training program on buprenorphine. SAMHSA maintains a list of upcoming DATA 2000-qualifying buprenorphine training sessions on the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov. These sessions include Web-based courses accessible from the physician's own computer. Detailed information about the DATA 2000 paradigm and the physician waiver process also can be found on the SAMHSA Buprenorphine Web site. Additionally, information can be obtained by contacting the SAMHSA Buprenorphine Information Center by phone at 866-BUP-CSAT (866-287-2728) or by e-mail at info@buprenorphine.samhsa.gov.

Preparing for Office-Based Opioid Treatment

Prior to embarking on the provision of office-based addiction treatment services, medical practices that will be new to this type of care should undertake certain preparations to ensure the highest quality experience for patients, providers, and staff. Providers and practice staff should have an appropriate level of training, experience, and comfort with this new form of treatment. Linkages with other medical and mental health professionals should be established to ensure the availability of comprehensive community-based treatment services.

Physician Training, Experience, and Comfort Level

Physicians who intend to treat opioid addiction should seek to establish a level of comfort and expertise with this form of care. A physician's comfort level in providing treatment for addiction will vary according to the physician and his or her practice situation. For example, a physician might choose to refer a patient with addiction and depression, depending on the severity of depression, whether a psychologist or psychiatrist is available in the area, and whether the patient can afford specialized mental health care, among other factors.

Proper training on the use of buprenorphine will be key to the successful introduction of this new treatment paradigm…

Expertise in treating opioid addiction includes knowledge of applicable practice standards or guidelines, familiarity with the evidence supporting the recommended treatments, protocols for primary treatment or referral of patients with certain complicating conditions (e.g., severe depression), and knowledge of any applicable regulations or laws. Physicians must become knowledgeable about the most up-to-date treatments for opioid addiction,

including pharmacotherapy, psychosocial interventions, self-help and mutual-help groups, and other appropriate treatments. Physicians who treat opioid-addicted patients with buprenorphine should participate in addiction medicine training and professional activities and should learn from other professionals in addiction treatment. Basic and ongoing training in addiction treatment will greatly enhance a physician's effectiveness in treating opioid addiction.

Each patient presents with different and usually complex needs. Physicians who treat patients with opioid addiction in the office-based setting must consider and plan for the full range of their patients' needs before initiating treatment. Candidates for buprenorphine treatment of opioid addiction should be assessed for a broad array of biopsychosocial needs in addition to opioid use and addiction, and should be treated and/or referred for help in meeting those needs.

Establishing Office Procedures

Before undertaking the provision of office-based buprenorphine treatment, physicians should make arrangements to provide comprehensive care and contingency plans for patients who may not be appropriate candidates for this treatment. In addition, physicians should arrange for other physicians with DATA 2000 waivers to be available to provide care to the treating physician's opioid addiction patients in the treating physician's absence (e.g., while on vacation).

Office policies and procedures for opioid addiction treatment should be established, written, and clearly communicated to staff members and patients. Staff members should be trained and educated about opioid addiction, addiction treatment, patient confidentiality (see "Confidentiality and Privacy" section below), medication treatments, nonpharmacological treatments, behavioral characteristics of addiction, and the medical approach to addiction treatment.

Common behaviors and defense mechanisms of addicted patients should be anticipated. Medication must be stored in a secure location, and the possibility of diversion must be minimized. Office items (e.g., prescription pads, syringes, needles) and staff possessions should be secured to minimize theft.

Establishing Treatment Linkages

Establishing linkages with other medical professionals is essential. Because patients addicted to opioids commonly have coexisting medical and psychiatric conditions, most physicians will need to establish linkages with other medical and mental health specialists, particularly those specializing in the evaluation and treatment of common comorbid conditions (e.g., hepatitis B and C, HIV, tuberculosis, mood disorders, anxiety disorders, personality disorders, risk of suicide and homicide). Physical examinations and laboratory evaluations will need to be completed either onsite or offsite from the office of the physician who provides office-based buprenorphine treatment.

An up-to-date listing of community referral resources (e.g., therapy groups, support groups, residential therapeutic communities, sober-living options) should be given to patients. Referral resource lists are available from the substance abuse agencies of some local and State governments. To maximize followthrough with referrals, it is most helpful if the physician has firsthand knowledge of these groups and programs. When referrals are made, compliance will increase if staff call to make appointments in the presence of patients. When making referrals to support groups, it is helpful to have an individual in the group who is willing to accompany the patient to his or her first meeting. Referrals to social workers and case managers are often beneficial in helping patients address legal, employment, and family issues.

Summary

Figure 6–1 summarizes the policies, procedures, and items that should be established or arranged for in a medical practice prior to initiating office-based opioid addiction treatment.

Confidentiality and Privacy

Prior to initiating office-based opioid addiction treatment, practice policies and procedures should be established that will guarantee the privacy and confidentiality of addiction treatment patients. Providers must comply with all applicable laws and regulations regarding the privacy and confidentiality of medical records in general, and of information pertaining to addiction treatment services in particular.

The privacy and confidentiality of individually identifiable information relating to patients receiving drug or alcohol treatment is protected by SAMHSA confidentiality regulation Title 42, Part 2 of the Code of Federal Regulations (42 C.F.R. Part 2). This regulation mandates that addiction treatment information in the possession of substance abuse treatment providers be handled with a greater degree of confidentiality than general medical information.

Occasionally, physicians will need to communicate with pharmacists and other healthcare providers about the addiction treatment of a particular patient (e.g., to verify a Suboxone® or Subutex® prescription). Regulation 42 C.F.R. Part 2 requires physicians providing opioid addiction treatment to obtain signed patient consent before disclosing individually identifiable addiction treatment information to any third party. A sample consent form with all the elements required by 42 C.F.R. Part 2 is included as appendix D. It is recommended that physicians have each new buprenorphine patient sign a copy of this form to prevent confidentiality problems at

Figure 6–1

Policies, Procedures, and Items for Medical Practices To Establish Prior to Initiating Office-Based Opioid Addiction Treatment

- Office policies and procedures for buprenorphine treatment
- Staff education and training
- Backup coverage for the practice
- Assurance of the privacy and confidentiality of addiction treatment information
- Linkages with qualified colleagues who will accept new referrals for buprenorphine treatment
- A referral network of medical specialists
- Timely physical examinations
- Linkages with medical treatment facilities, including opioid treatment programs
- A referral network of psychologists and psychiatrists with expertise in addictions, affective disorders, and chronic pain
- Linkages with addiction and psychiatric treatment programs
- Listing of community referral resources, including specific self-help groups who would welcome buprenorphine patients (e.g., Self Management and Recovery Training [SMART] Recovery, Moderation Management)
- Online/Internet listings of self-help groups (e.g., SMART Recovery, Moderation Management) that are accepting of individuals in recovery who are using medications as a part of that recovery

pharmacies when patients present with buprenorphine prescriptions. It is particularly important to obtain patient consent when telephoning or faxing prescriptions to pharmacies, as this information constitutes disclosure of the patient's addiction treatment. When physicians directly transmit prescriptions to pharmacies, further redisclosure of patient-identifying information by the pharmacy is prohibited, unless signed patient consent is obtained by the pharmacy. Regulation 42 C.F.R. Part 2 does not apply to pharmacies, however, when the patient delivers a buprenorphine prescription without telephone confirmation or other direct communication from a physician to the pharmacist.

The Health Insurance Portability and Accountability Act (HIPAA) of 1996, Public Law 104-191 (see http://aspe.hhs.gov/admnsimp/pl104191.htm), which amends the Internal Revenue Service Code of 1986, mandates standardization of exchange formats for patient health, administrative, and financial data; requires development of unique identifiers for individuals, employers, health plans, and healthcare providers; and establishes security standards for protecting the confidentiality and integrity of individually identifiable health information. SAMHSA has prepared a document titled *Comparison Between the Confidentiality of Alcohol and Substance Abuse Patient Records (42 C.F.R. Part 2) and the Health Insurance Portability and Accountability Act 1996*. This document and a number of other HIPAA technical assistance tools are available on the SAMHSA HIPAA Web pages at http://www.hipaa.samhsa.gov/. See also the SAMHSA Treatment Assistance Publication (TAP) 13 *Confidentiality of Patient Records for Alcohol and Other Drug Treatment* (Lopez 1994), available on the SAMHSA Treatment Improvement Exchange Web site at http://www.treatment.org/taps/index.html. Additionally, the Subutex® and Suboxone® package labels (available on the FDA Web site at http://www.fda.gov/cder/drug/infopage/subutex_suboxone/default.htm) also contain information on Federal confidentiality rules and regulations. Physicians should also consult with their State medical authorities concerning privacy and confidentiality rules in their locales. Figure 6–2 lists some of the privacy and confidentiality issues that can arise in the course of addiction treatment.

Buprenorphine Use in OTPs

On May 22, 2003, SAMHSA announced an interim final rule permitting OTPs serving individuals addicted to opioids to offer

Figure 6–2

Privacy and Confidentiality Issues in Addiction Treatment

- Information covered by the doctor/patient privilege
- Circumstances in which confidential information is protected from disclosure
- Exceptions to State laws protecting medical information
- Duty to report
- Communications with third parties (e.g., families, employers, allied healthcare providers, third-party payers, law-enforcement officers, responses to subpoenas)

buprenorphine treatment along with methadone and levo-alpha-acetyl-methadol (LAAM). The rule enables OTPs that are certified by SAMHSA to provide Subutex® and Suboxone® for opioid maintenance or detoxification treatment.

The provision of opioid addiction treatment with Subutex® and Suboxone® in SAMHSA-certified OTPs does not require a DATA 2000 waiver. Additionally, such treatment is not subject to the 30-patient limit that applies to individual physicians and group practices providing opioid addiction treatment outside the OTP system under the authority of a DATA 2000 waiver. The provision of opioid addiction treatment with Subutex® or Suboxone® in treatment settings other than OTPs, even by physicians who are licensed to work in OTPs, does require a DATA 2000 waiver and is subject to the 30-patient limit for individual physicians and group practices.

OTPs providing Subutex® and Suboxone® for opioid maintenance or detoxification treatment must conform to the Federal opioid treatment standards set forth under 42 C.F.R. § 8.12. These regulations require that OTPs provide medical, counseling, drug abuse testing, and other services to patients admitted to treatment. To offer Subutex® and Suboxone®, OTPs need to modify their registration with the DEA to add Schedule III narcotics to their registration certificates. OTPs can initiate this streamlined process by fax or letter. The letter should include the OTP's DEA registration number and request that the registration be amended to list Schedule III narcotic drugs. The letter must be signed by the program sponsor (program director) or medical director. Further information about this process can be found on the DEA Drug Registration Web site at http://www.deadiversion.usdoj.gov/drugreg/change_requests/sched_change.htm.

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Appendix B Assessment and Screening Instruments

Several of the following drug and alcohol assessment and screening instruments are available online at: http://www.niaaa.nih.gov/publications/publications.htm.

General

- Addiction Severity Index (ASI) (McLellan et al. 1980) (http://www.tresearch.org and http://www.niaaa.nih.gov/publications/asi.htm)
- Substance Use Disorders Diagnostic Schedule (SUDDS-IV) (Hoffmann and Harrison 2002) (http://www.evinceassessment.com/product_sudds.html)

Readiness to Change

See appendix G.

Screening Instruments

Drug Abuse Screening Test (DAST-10), Drug Use Questionnaire

The following questions concern information about your possible involvement with drugs not including alcoholic beverages during the past 12 months. Carefully read each statement and decide if your answer is “Yes” or “No.” Then circle the appropriate response beside the question.

In the following statements "drug abuse" refers to

- The use of prescribed or over-the-counter drugs in excess of the directions, and
- Any nonmedical use of drugs.
- The various classes of drugs may include cannabis (e.g., marijuana, hashish), solvents (e.g., paint thinner), tranquilizers (e.g., Valium), barbiturates, cocaine, stimulants (e.g., speed), hallucinogens (e.g., lysergic acid diethylamide [LSD]), or narcotics (e.g., heroin). Remember that the questions do not include alcoholic beverages.

Please answer every question. If you have difficulty with a question, then choose the response that is mostly right.

These Questions Refer to the Past 12 Months			
1.	Have you used drugs other than those required for medical reasons?	Yes	No
2.	Do you abuse more than one drug at a time?	Yes	No
3.	Are you always able to stop using drugs when you want to?	Yes	No
4.	Have you ever had blackouts or flashbacks as a result of drug use?	Yes	No
5.	Do you ever feel bad or guilty about your drug use?	Yes	No
6.	Does your spouse (or parents) ever complain about your involvement with drugs?	Yes	No
7.	Have you neglected your family because of your use of drugs?	Yes	No
8.	Have you engaged in illegal activities in order to obtain drugs?	Yes	No
9.	Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	Yes	No
10.	Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding)?	Yes	No

Interpretation (Each "Yes" response = 1)

Score	Degree of Problems Related to Drug Abuse	Suggested Action
0	No Problems Reported	None At This Time
1–2	Low Level	Monitor, Reassess At A Later Date
3–5	Moderate Level	Further Investigation
6–8	Substantial Level	Intensive Assessment

Source: Adapted from Addictive Behaviors, 7(4), Skinner, H.A. The drug abuse screening test, 363–371, copyright 1982, with permission from Elsevier. Available online at http://www.drugabuse.gov/Diagnosis-Treatment/DAST10.html.

Skinner Trauma History

Since your 18th birthday, have you

Had any fractures or dislocations to your bones or joints?
Been injured in a road traffic accident?
Injured your head?
Been injured in an assault or fight (excluding injuries during sports)?
Been injured after drinking?

A score of two or more positive responses to the five questions has been shown to indicate a high probability of excessive drinking or alcohol abuse.

Source: Skinner et al. 1984, reprinted with permission from American College of Physicians–American Society of Internal Medicine (ACP–ASIM).

CAGE Questionnaire

Have you ever felt you ought to **C**ut down on your drinking?
Have people **A**nnoyed you by criticizing your drinking?
Have you ever felt bad or **G**uilty about your drinking?
Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye-opener)?

One or more "yes" responses constitute a positive screening test. Note, however, that due to language barriers, individual interpretation of the questions, or other confounding factors, individuals answering "no" to all CAGE questions may still be at risk due to elevated drinking levels.

Source: Maisto et al. 2003.

CAGE-AID: The CAGE Questions Adapted To Include Drugs

Have you felt you ought to **C**ut down on your drinking or drug use?
Have people **A**nnoyed you by criticizing your drinking or drug use?
Have you felt bad or **G**uilty about your drinking or drug use?
Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?

One or more "yes" responses constitute a positive screening test. Note, however, that due to language barriers, individual interpretation of the questions, or other confounding factors, individuals answering "no" to all CAGE-AID questions may still be at risk due to elevated drinking or drug use levels.

Source: Brown and Rounds 1995.

The TWEAK Questionnaire

Tolerance: (a) How many drinks can you hold, or (b) How many drinks does it take before you begin to feel the first effects of the alcohol?

Worried: Have close friends or relatives worried or complained about your drinking in the past year?

Eye openers: Do you sometimes take a drink in the morning when you first get up?

Amnesia: Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember?

Kut down: Do you sometimes feel the need to cut down on your drinking?

The TWEAK questionnaire was originally developed to screen for risk drinking during pregnancy (Russell et al. 1991). It can also be used to screen for harmful drinking in the general population (Chan et al. 1993).

Scoring: A 7-point scale is used to score the test. The Tolerance question scores 2 points if (a) the patient reports he or she can hold more than five drinks without falling asleep or passing out, or (b) if it is reported that three or more drinks are needed to feel high. A positive response to the Worry question scores 2 points. A positive response to the last three questions scores 1 point each.

A total score of 3 or 4 usually indicates harmful drinking. In an obstetric patient, a total score of 2 or more indicates the likelihood of harmful drinking.

Source: The National Institute on Alcohol Abuse and Addiction Web site at http://www.niaaa.nih.gov/publications/tweak.htm

The Alcohol Use Disorders Identification Test (AUDIT): Interview Version

1. How often do you have a drink* containing alcohol?
   [ ] Never (0) [Skip to Questions 9–10]
   [ ] Monthly or less (1)
   [ ] 2 to 4 times a month (2)
   [ ] 2 to 3 times a week (3)
   [ ] 4 or more times a week (4)

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   [ ] 1 or 2 (0)
   [ ] 3 or 4 (1)
   [ ] 5 or 6 (2)
   [ ] 7, 8, or 9 (3)
   [ ] 10 or more (4)

3. How often do you have six or more drinks on one occasion?
   [ ] Never (0)
   [ ] Less than monthly (1)
   [ ] Monthly (2)
   [ ] Weekly (3)
   [ ] Daily or almost daily (4)

[Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0]

4. How often during the last year have you found that you were unable to stop drinking once you had started?
   [ ] Never (0)
   [ ] Less than monthly (1)
   [ ] Monthly (2)
   [ ] Weekly (3)
   [ ] Daily or almost daily (4)

5. How often during the last year have you failed to do what was normally expected of you because of drinking?
   [ ] Never (0)
   [ ] Less than monthly (1)
   [ ] Monthly (2)
   [ ] Weekly (3)
   [ ] Daily or almost daily (4)

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   [ ] Never (0)
   [ ] Less than monthly (1)
   [ ] Monthly (2)
   [ ] Weekly (3)
   [ ] Daily or almost daily (4)

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   [ ] Never (0)
   [ ] Less than monthly (1)
   [ ] Monthly (2)
   [ ] Weekly (3)
   [ ] Daily or almost daily (4)

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   [ ] Never (0)
   [ ] Less than monthly (1)
   [ ] Monthly (2)
   [ ] Weekly (3)
   [ ] Daily or almost daily (4)

9. Have you or someone else been injured as the result of your drinking?
   [ ] No (0)
   [ ] Yes, but not in the last year (1)
   [ ] Yes, during the last year (2)

10. Has a relative, friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?
   [ ] No (0)
   [ ] Yes, but not in the last year (1)
   [ ] Yes, in the last year (2)

Record the total of the specific items. [ ]

*In determining the response categories it has been assumed that one drink contains 10 g alcohol. In countries where the alcohol content of a standard drink differs by more than 25 percent from 10 g, the response category should be modified accordingly.

Source: Babor et al. 2001. Available at http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf

A self-report version of the AUDIT is also available in Babor et al. 2001.

Scoring and Interpretation of the AUDIT

The minimum score (for nondrinkers) is 0 and the maximum possible score is 40. A score of 8 is indicative of hazardous and harmful alcohol use, and possibly of alcohol dependence. Scores of 8–15 indicate a medium level and scores of 16 and above a high level of alcohol problems. Babor et al. (2001) recommend a cutoff score of 7 for women and individuals over 65 years of age; Bradley et al. (1998) recommended an even lower cutoff score of 4 points for women. For patients who are resistant, uncooperative, or noncommunicative, a clinical screening procedure (described by Babor et al. 2001) may be necessary.

Michigan Alcoholism Screening Test (MAST)

0.	Do you enjoy a drink now and then?	**YES**	**NO**
(2) 1.	*Do you feel you are a normal drinker? (By normal we mean you drink less than or as much as most other people)	**YES**	**NO**
(2) 2.	Have you ever awakened the morning after some drinking the night before and found that you could not remember a part of the evening?	**YES**	**NO**
(1) 3.	Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking?	**YES**	**NO**
(2) 4.	*Can you stop drinking without a struggle after one or two drinks?	**YES**	**NO**
(1) 5.	Do you ever feel guilty about your drinking?	**YES**	**NO**
(2) 6.	*Do friends or relatives think you are a normal drinker?	**YES**	**NO**
(2) 7.	*Are you able to stop drinking when you want to?	**YES**	**NO**
(5) 8.	Have you ever attended a meeting of Alcoholics Anonymous (AA)?	**YES**	**NO**
(1) 9.	Have you gotten into physical fights when drinking?	**YES**	**NO**
(2) 10.	Has your drinking ever created problems between you and your wife, husband, a parent, or other relative?	**YES**	**NO**
(2) 11.	Has your wife, husband (or other family member) ever gone to anyone for help about your drinking?	**YES**	**NO**
(2) 12.	Have you ever lost friends because of your drinking?	**YES**	**NO**
(2) 13.	Have you ever gotten into trouble at work or school because of drinking?	**YES**	**NO**
(2) 14.	Have you ever lost a job because of drinking?	**YES**	**NO**
(2) 15.	Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?	**YES**	**NO**
(1) 16.	Do you drink before noon fairly often?	**YES**	**NO**
(2) 17.	Have you ever been told you have liver trouble? Cirrhosis?	**YES**	**NO**
(2) 18.	**After heavy drinking have you ever had delirium tremens (DTs) or severe shaking or heard voices or seen things that really weren't there?	**YES**	**NO**
(5) 19.	Have you ever gone to anyone for help about your drinking?	**YES**	**NO**
(5) 20.	Have you ever been in a hospital because of drinking?	**YES**	**NO**
(2) 21.	Have you ever been a patient in a psychiatric hospital or on a psychiatric ward of a general hospital where drinking was part of the problem that resulted in hospitalization?	**YES**	**NO**
(2) 22.	Have you ever been seen at a psychiatric or mental health clinic or gone to any doctor, social worker, or clergyman for help with any emotional problem where drinking was part of the problem?	**YES**	**NO**
(2) 23.	***Have you ever been arrested for drunk driving, driving while intoxicated, or driving under the influence of alcoholic beverages? If YES, how many times? _____	**YES**	**NO**
(2) 24.	Have you ever been arrested, or taken into custody, even for a few hours, because of other drunk behavior? If YES, how many times?_____	**YES**	**NO**

* Alcoholic response is negative
** 5 points for each DT
*** 2 points for each arrest

MAST Scoring System

In general, five points or more would place the subject in alcoholic category. Four points would be suggestive of alcoholism, and three points or fewer would indicate the subject is not alcoholic (Selzer 1971).

Source: American Journal of Psychiatry, 127, 1653–1658 (1971). Copyright (1971). The American Psychiatric Association, http://ajp.psychiatryonline.org. Reprinted by permission. See http://www.niaaa.nih.gov/publications/mast.htm.

Self-Administered Short Michigan Alcoholism Screening Test (SMAST)

Patient Name: _____

Date of Birth: _____

Date of Administration: _____

1. Do you feel you are a normal drinker? (By normal we mean you drink less than or as much as most other people.)	**YES**	**NO**
2. Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking?	**YES**	**NO**
3. Do you ever feel guilty about your drinking?	**YES**	**NO**
4. Do friends or relatives think you are a normal drinker?	**YES**	**NO**
5. Are you able to stop drinking when you want to?	**YES**	**NO**
6. Have you ever attended a meeting of Alcoholics Anonymous?	**YES**	**NO**
7. Has drinking ever created problems between you and your wife, husband, a parent, or other near relative?	**YES**	**NO**
8. Have you ever gotten into trouble at work or school because of drinking?	**YES**	**NO**
9. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?	**YES**	**NO**
10. Have you ever gone to anyone for help about your drinking?	**YES**	**NO**
11. Have you ever been in a hospital because of drinking?	**YES**	**NO**
12. Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?	**YES**	**NO**
13. Have you ever been arrested, even for a few hours, because of other drunken behavior?	**YES**	**NO**

Source: Adapted from Selzer et al. 1975. Reprinted with permission from the *Journal of Studies on Alcohol*.

SMAST Scoring System

Each of the 13 items on the Short MAST is scored 1 (one) or 0 (zero), with questions 1, 4, and 5 scored 1 for each "no" answer, and the other items scored 1 for each "yes" answer. A score of 2 indicates possible alcoholism; a score of 3 or greater indicates probable alcoholism.

Withdrawal Assessments

Narcotic Withdrawal Scale

Fultz and Senay (1975); (Table 1 page 816) used a grading scheme for hospitalized patients undergoing opiate withdrawal to determine initial methadone therapy as follows:

Grade	Physical Findings	Initial Dose of Methadone
1	Lacrimation and/or rhinorrhea Diaphoresis Yawning Restlessness Insomnia	5 mg
2	Dilated pupils Piloerection Muscle twitching and/or myalgia Arthralgias Abdominal pain	10 mg
3	Tachycardia Hypertension Tachypnea Fever Anorexia or nausea Extreme restlessness	15 mg
4	Diarrhea and/or vomiting Dehydration Hyperglycemia Hypotension Curled-up position	20 mg

Source: Fultz and Senay 1975, reprinted with permission from American College of Physicians–American Society of Internal Medicine (ACP–ASIM).

The Clinical Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms

The Clinical Institute Narcotic Assessment (CINA) Scale measures 11 signs and symptoms commonly seen in patients during narcotic withdrawal. This can help to gauge the severity of the symptoms and to monitor changes in the clinical status over time.

PARAMETERS	FINDINGS	POINTS
Parameters based on Questions and Observation:		
(1) abdominal changes: Do you have any pains in your abdomen?	No abdominal complaints; normal bowel sounds Reports waves of crampy abdominal pain Crampy abdominal pain; diarrhea; active bowel sounds	0 1 2
(2) changes in temperature: Do you feel hot or cold?	None reported Reports feeling cold; hands cold and clammy to touch Uncontrolled shivering	0 1 2
(3) nausea and vomiting: Do you feel sick in your stomach? Have you vomited?	No nausea or vomiting Mild nausea; no retching or vomiting Intermittent nausea with dry heaves Constant nausea; frequent dry heaves and/or vomiting	0 2 4 6
(4) muscle aches: Do you have any muscle cramps?	No muscle aching reported; arm and neck muscles soft at rest Mild muscle pains Reports severe muscle pains; muscles in legs arms or neck in constant state of contraction	0 1 3
Parameters based on Observation Alone:		
(5) goose flesh	None visible Occasional goose flesh but not elicited by touch; not permanent Prominent goose flesh in waves and elicited by touch Constant goose flesh over face and arms	0 1 2 3
(6) nasal congestion	No nasal congestion or sniffling Frequent sniffling Constant sniffling watery discharge	0 1 2
(7) restlessness	Normal activity Somewhat more than normal activity; moves legs up and down; shifts position occasionally Moderately fidgety and restless; shifting position frequently Gross movement most of the time or constantly thrashes about	0 1 2 3
(8) tremor	None Not visible but can be felt fingertip to fingertip Moderate with patient's arm extended Severe even if arms not extended	0 1 2 3
(9) lacrimation	None Eyes watering; tears at corners of eyes Profuse tearing from eyes over face	0 1 2
(10) sweating	No sweat visible Barely perceptible sweating; palms moist Beads of sweat obvious on forehead Drenching sweats over face and chest	0 1 2 3
(11) yawning	None Frequent yawning Constant uncontrolled yawning	0 1 2
TOTAL SCORE	[Sum of points for all 11 parameters]	

Minimum score=0, Maximum score=31. The higher the score, the more severe the withdrawal syndrome. Percent of maximal withdrawal symptoms=((total score)/31) x 100%.
Source: Adapted from Peachey, J.E., and Lei, H. Assessment of opioid dependence with naloxone. *British Journal of Addiction* 83(2):193–201, 1988. Reprinted with permission from Blackwell Publishing, Ltd.

Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptoms. Rate just on the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient Name:	**Date:**	**Time:**
Reason for this assessment:		
1. Resting pulse rate: _____ beats/minute Measured after the patient is sitting or lying for one minute. 0 Pulse rate 80 or below 1 Pulse rate 81–100 2 Pulse rate 101–120 4 Pulse rate greater than 120	**7. GI upset:** *over last half hour* 0 No GI symptoms 1 Stomach cramps 2 Nausea or loose stool 3 Vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting	
2. Sweating: *over past half hour not accounted for by room temperature of patient activity* 0 No reports of chills or flushing 1 Subjective reports of chills or flushing 2 Flushed or observable moisture on face 3 Beads of sweat on brow or face 4 Sweat streaming off face	**8. Tremor:** *observation of outstretched hands* 0 No tremor 1 Tremor can be felt, but not observed 2 Slight tremor observable 4 Gross tremor or muscle twitching	
3. Restlessness: *observation during assessment* 0 Able to sit still 1 Reports difficulty sitting still, but is able to do so 3 Frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	**9. Yawning:** *observation during assessment* 0 No yawning 1 Yawning once or twice during assessment 2 Yawning three or more times during assessment 4 Yawning several times/minute	
4. Pupil size 0 Pupils pinned or normal size for room light 1 Pupils possibly larger than normal for room light 2 Pupils moderately dilated 5 Pupils so dilated that only the rim of the iris is visible	**10. Anxiety or irritability** 0 None 1 Patient reports increasing irritability or anxiousness 2 Patient obviously irritable, anxious 4 Patient so irritable or anxious that participation in the assessment is difficult	
5. Bone or joint aches: *if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored.* 0 Not present 1 Mild diffuse discomfort 2 Patient reports severe diffuse aching of joints/muscles 4 Patient is rubbing joints or muscles and is unable to sit still because of discomfort	**11. Gooseflesh skin** 0 Skin is smooth 3 Piloerection of skin can be felt or hairs standing up on arms 5 Prominent piloerection	
6. Runny nose or tearing: *not accounted for by cold symptoms or allergies* 0 Not present 1 Nasal stuffiness or unusually moist eyes 2 Nose running or tearing 4 Nose constantly running or tears streaming down cheeks	Total Score: _____ [The total score is the sum of all 11 items.] Initials of person completing assessment: ___	

Score: 5–12=Mild; 13–24=Moderate; 25–36=Moderately severe; >36=Severe withdrawal

Source: Adapted from Wesson et al. 1999. Reprinted with permission.

Subjective Opiate Withdrawal Scale (SOWS)

Instructions: Answer the following statements as accurately as you can. Circle the answer that best fits the way you feel now.

0=not at all
1=a little
2=moderately
3=quite a bit
4=extremely

	Not at all	A little	Moderately	Quite a bit	Extremely
1 I feel anxious.	0	1	2	3	4
2 I feel like yawning.	0	1	2	3	4
3 I'm perspiring.	0	1	2	3	4
4 My eyes are tearing.	0	1	2	3	4
5 My nose is running.	0	1	2	3	4
6 I have goose flesh.	0	1	2	3	4
7 I am shaking.	0	1	2	3	4
8 I have hot flashes.	0	1	2	3	4
9 I have cold flashes.	0	1	2	3	4
10 My bones and muscles ache.	0	1	2	3	4
11 I feel restless.	0	1	2	3	4
12 I feel nauseous.	0	1	2	3	4
13 I feel like vomiting.	0	1	2	3	4
14 My muscles twitch.	0	1	2	3	4
15 I have cramps in my stomach.	0	1	2	3	4
16 I feel like shooting up now.	0	1	2	3	4

The Subjective Opiate Withdrawal Scale (SOWS) consist of 16 symptoms rated in intensity by patients on a 5-point scale of intensity as follows: 0=not at all, 1=a little, 2=moderately, 3=quite a bit, 4=extremely. The total score is a sum of item ratings, and ranges from 0 to 64.

Source: Reprinted from Handelsman et al. 1987, p. 296, by courtesy of Marcel Dekker, Inc.

Other Sources: Gossop 1990; Bradley 1987.

Addiction Research Foundation Clinical Institute for Withdrawal Assessment (CIWA-Ar)

Patient:	**Date:**	**Time:** (24 hour clock, midnight = 00:00)

NAUSEA AND VOMITING—Ask "Do you feel sick to your stomach? Have you vomited?"
Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES—Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?"
Observation.
0 none
1 mild itching, pins and needles, burning or numbness
2 very mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

TREMOR—Arms extended and fingers spread apart.
Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

AUDITORY DISTURBANCES—Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"
Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

PAROSYSMAL SWEATS—*Observation*.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

VISUAL DISTURBANCES—Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

ANXIETY—Ask "Do you feel nervous?"
Observation.
0 no anxiety, at ease
1 mildly anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions.

HEADACHE, FULLNESS IN HEAD—Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

AGITATION—*Observation*.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM—Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place and/or person

Total CIWAr-Score	
Rater's Initials	
Maximum Possible Score	67

Source: Sullivan et al. 1989.

Appendix C
DSM-IV-TR Material

Criteria for Substance Dependence

A **maladaptive pattern of substance use**, leading to clinically significant impairment or distress, **as manifested by** three (or more) of the following, occurring at any time in the same 12-month period **(emphasis ours)**:

(1) Tolerance, as defined by either of the following:

a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect

or

b. Markedly diminished effect with continued use of the same amount of the substance

(2) Withdrawal, as manifested by either of the following:

a. The characteristic withdrawal syndrome for the substance

or

b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) The substance is often taken in larger amounts or over a longer period than was intended

(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) A great deal of time is spent on activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use

(7) The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Specify if:

With Physiological Dependence: Evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present)

Without Physiological Dependence: No evidence of tolerance or withdrawal (i.e., neither Item 1 nor 2 is present)

Substance Dependence Course Specifiers

Six course specifiers are available for Substance Dependence. The four Remission specifiers can be applied only after none of the criteria for Substance Dependence or Substance Abuse have been present for at least 1 month. The definition of these four types of Remission is based on the interval of time that has elapsed since the cessation of Dependence (Early versus Sustained Remission) and whether there is continued presence of one or more of the items included in the criteria sets for Dependence or Abuse (Partial versus Full Remission). Because the first 12 months following Dependence is a time of particularly high risk for relapse, this period is designated Early Remission. After 12 months of early Remission have passed without relapse to Dependence, the person enters into Sustained Remission. For both Early Remission and Sustained Remission, a further designation of Full is given if no criteria for Dependence or Abuse have been met during the period of remission; a designation of Partial is given if at least one of the criteria for Dependence or Abuse has been met, intermittently or continuously, during the period of remission. The differentiation of Sustained Full Remission from recovered (no current Substance Abuse Disorder) requires consideration of the length of time since the last period of disturbance, the total duration of the disturbance, and the need for continued evaluation. If, after a period of remission or recovery, the individual again becomes dependent, the application of the Early Remission specifier requires that there again be at least 1 month in which no criteria for Dependence or Abuse are met.

Two additional specifiers have been provided: On Agonist Therapy and In a Controlled Environment. For an individual to qualify for Early Remission after cessation of agonist therapy or release from a controlled environment, there must be a 1-month period in which none of the criteria for Dependence of Abuse are met.

The following Remission specifiers can be applied only after no criteria for Dependence or Abuse have been met for at least 1 month. Note that these specifiers do no apply if the individual is on agonist therapy or in a controlled environment (see below).

Early Full Remission: This specifier is used if, for at least 1 month, but for less than 12 months, no criteria for Dependence or Abuse have been met.

Early Partial Remission: This specifier is used if, for at least 1 month, but less than 12 months, one or more criteria for Dependence or Abuse have been met (but the full criteria for Dependence have not been met).

Sustained Full Remission: This specifier is used if none of the criteria for Dependence or Abuse have been met at any time during a period of 12 months or longer.

Sustained Partial Remission: This specifier is used if full criteria for Dependence have not been met for a period of 12 months or longer; however, one or more criteria for Dependence or Abuse have been met.

On Agonist Therapy: This specifier is used if the individual is on a prescribed agonist medication, and no criteria for Dependence or Abuse have been met for that class of medication for at least the past month (except tolerance to, or withdrawal from, the agonist). This category also applies to those being treated for Dependence using a partial agonist or an agonist/antagonist.

In a Controlled Environment: This specifier is used if the individual is in an environment where access to alcohol and controlled substances is restricted, and no criteria for

Dependence or Abuse have been met for at least the past month. Examples of these environments are closely supervised and substance-free jails, therapeutic communities, or locked hospital units.

Criteria for Substance Abuse

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

- Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household
- Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
- Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequence of intoxication, physical fights)

The symptoms have never been met the criteria for Substance Dependence for this class of substance.

Opioid Dependence

Refer, in addition, to the text and criteria for Substance Dependence. Most individuals with Opioid Dependence have significant levels of tolerance and will experience withdrawal on abrupt discontinuation of opioid substances. Opioid Dependence includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if a general medical condition is present that requires opioid treatment, that are used in doses that are greatly in excess of the amount needed for pain relief. Persons with Opioid Dependence tend to develop such regular patterns of compulsive drug use that daily activities are typically planned around obtaining and administering opioids. Opioids are usually purchased on the illegal market but may also be obtained from physicians by faking or exaggerating general medical problems, or by receiving simultaneous prescriptions from several physicians. Health care professionals with Opioid Dependence will often obtain opioids by writing prescriptions for themselves or by diverting opioids that have been prescribed for patients or from pharmacy supplies.

Other DSM-IV Substance-Related Disorders

ICD-9-CM

292.82	Persisting Dementia
292.83	Persisting Amnestic Disorder
292.11	Psychotic Disorder with Delusions
292.12	Psychotic Disorder with Hallucinations
292.84	Mood Disorder
292.89	Anxiety Disorder
292.89	Sleep Disorder
292.89	Sexual Dysfunction
292.89	Persisting Perception Disorder (Flashbacks)
292.9	Disorder Not Otherwise Specified

Substance Related Disorders

305.01	Alcohol abuse, continuous
305.02	Alcohol abuse, episodic
305.03	Alcohol abuse, remission
305.00	Alcohol abuse, unspec.
303.00	Alcohol intoxication, acute, unspec.
291.81	Alcohol withdrawal
303.91	Alcoholism, chronic, continuous
304.41	Amphetamine dependence, continuous
304.11	Barbiturate dependence, continuous
305.22	Cannabis abuse, episodic
304.31	Cannabis dependence, continuous
305.62	Cocaine abuse, episodic
304.21	Cocaine dependence, continuous
305.90	Drug abuse, unspec.
305.92	Drug abuse, unspec., episodic
304.90	Drug dependence, unspec.
292.11	Drug-induced paranoia
305.52	Opioid abuse, episodic
304.01	Opioid dependence, continuous
305.1	Tobacco abuse

Appendix D
Consent to Release of Information Under Title 42, Part 2, Code of Federal Regulations

The privacy and confidentiality of individually identifiable drug or alcohol treatment information is protected by SAMHSA confidentiality regulation Title 42, Part 2 of the Code of Federal Regulations (42 C.F.R. Part 2). This regulation requires that physicians providing opioid addiction treatment obtain signed patient consent before disclosing individually identifiable addiction treatment information to any third party. On the next page is a sample consent form containing all the data elements required by 42 C.F.R. Part 2.

1. I (name of patient) _____

2. Authorize: Dr. _____

3. To disclose: (kind and amount of information to be disclosed)
Any information needed to confirm the validity of my prescription and for submission for payment for the prescription.

4. To: (name or title of the individual or organization to which disclosure is to be made)
The dispensing pharmacy to which I present my prescription or to which my prescription is called/sent/faxed, as well as to third party payors.

5. For (purpose of the disclosure)
Assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.

6. Date (on which this consent is signed)

7. Signature of patient

8. Signature of parent or guardian (where required)

9. Signature of individual authorized to sign in lieu of the patient (where required)

10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate on: (specific date, event, or condition)

Termination of treatment.

(c) Expired, deficient, or false consent. A disclosure may not be made on the basis of a consent which: (1) Has expired; (2) on its face substantially fails to conform to any of the requirements set forth in paragraph (a) of this section; (3) is known to have been revoked; or (4) is known, or through a reasonable effort could be known, by the individual holding the records to be materially false. (Approved by the Office of Management and Budget under control number 0930-0099.)

Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement: This information has been disclosed to you from records protected by Federal confidentiality rules (Title 42, Part 2, Code of Federal Regulations [42 C.F.R. Part 2]). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the individual to whom it pertains or as otherwise permitted by 42 C.F.R. Part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose.

Appendix E Clinical Toolbox: Chapter 3 Supplemental Information

Motivational Interviewing and Motivational Enhancement Therapy

A number of engagement and motivation strategies have been employed successfully in opioid addiction therapy. This section discusses briefly one such approach: motivational interviewing and motivational enhancement therapy (MET).

MET assumes that a patient is responsible for and capable of changing his or her behavior, and the MET therapist focuses on helping a patient mobilize his or her own inner resources. The basic motivational principles utilized in MET are expression of empathy, the development of discrepancy, avoiding argumentation, rolling with resistance, and supporting self-efficacy. Motivation for change is developed by eliciting self-motivational statements, listening with empathy, questioning, presenting personal feedback, affirming the patient, handling resistance, and reframing.

MET is a specific application of motivational interviewing that was developed for use in the treatment of alcohol abuse. In this brief, two- to four-session treatment approach, counselors first guide patients through an examination of the pros and cons of their drug use and of the difference between where they are and where they want to be, in an attempt to lead them to state their desire to change—the first step in recovery. Counselors then strengthen patients' commitment to change by helping them to identify their goals for recovery and to determine ways to reach these goals. Motivational interviewing can be used as a

stand-alone counseling approach, but more often it is used as a first step in the recovery process and is followed by other interventions. It can also be incorporated into subsequent treatment sessions to bolster patients' motivation as needed.

Additional information about motivational interviewing and MET can be found on the Motivational Interviewing Page at http://www.motivationalinterview.org and in Center for Substance Abuse Treatment (CSAT) TIP 35: *Enhancing Motivation for Change in Substance Use Disorder Treatment* (CSAT 1999*b*). (See http://www.kap.samhsa.gov/products/manuals/index.htm.)

FRAMES

Brief interventions by physicians or allied health professionals can be effective measures in opioid addiction therapy. Effective brief interventions should include the following six elements: feedback, responsibility, advice, menu of strategies, empathy, and self-efficacy (Miller and Sanchez 1994). These elements are commonly referred to using the acronym FRAMES, and are further described in figure E–1. Additional information about brief interventions is found in CSAT TIP 34 *Brief Intervention and Brief Therapies for Substance Abuse* (CSAT 1999*a*). (See http://www.kap.samhsa.gov/products/manuals/index.htm.)

Details of Taking a Comprehensive Patient History in Opioid Addiction Assessment

History of Drug Use

What substances have been used over time? Begin with the first psychoactive substance used (licit or illicit, prescribed or nonprescribed), including nicotine and caffeine. Ask about the first use of all drugs: age at first use, drugs used, description of the experiences and the situations, amounts used, feelings, complications, and results. "How old were you when you first tried alcohol or any other drugs? Describe the experience to me."

Ask about all psychoactive substances: alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine (PCP), sedatives, hypnotics, anxiolytics, and others. What substances has the patient ever used? When were each of these first used? What were the effects? What has happened over time? Focus on opioid use, progression of problems, and recent symptoms in patients being considered for buprenorphine treatment.

Effects of the Drugs Over Time

Explore the pattern of use of each substance. What has been the evolution and progression of use over time? Determine the frequency of use, amount of drugs used, route(s) used, progression of symptoms, and social context(s) of use. Has the patient attempted to cut down or control use; taken greater amounts of drugs or over a longer period than intended; spent much time using, obtaining drugs, or recovering from use? Has the patient had blackouts, shakes, withdrawal symptoms, compulsivity of use, and/or craving? Has he or she injected drugs; reduced or abandoned important activities as a consequence of use; and/or continued to use despite problems or consequences? If so, give examples.

When did regular opioid use begin? Does the patient have to use to feel "normal"? Describe periods of heaviest use. Explore in detail the pattern of use during the weeks prior to evaluation, including the amount and time of last use. When did he or she last consume alcohol or ingest or inject drugs? What was used? How much? What were the effects of the last drugs used?

Figure E–1

FRAMES: Elements of Brief Interventions

- **FEEDBACK** of personal risk or impairment. Most successful brief interventions provide clients with some form of feedback of the results of their assessment of alcohol and other drugs.
- Emphasis on personal **RESPONSIBILITY** for change. Many brief interventions advise patients that drinking is their own responsibility and choice. The implicit or explicit message is that "What you do about your drinking is up to you." Perceived control has been recognized as an element of motivation for behavior change and maintenance (Miller 1985).
- Clear **ADVICE** to change. Effective brief interventions contain explicit verbal or written advice to reduce or stop drinking. In fact, advice has been described as the essence of the brief intervention (Edwards et al. 1977).
- A **MENU** of alternative change options. Effective brief interventions seldom advise a single approach, but rather a general goal or a range of options. Presumably, this broad approach increases the likelihood that an individual will find an approach appropriate to his or her situation.
- Therapeutic **EMPATHY** as a counseling style. Successful interventions have emphasized a warm, reflective, empathic, and understanding approach. No reports of effective brief counseling contain aggressive, authoritarian, or coercive elements.
- Enhancement of client **SELF-EFFICACY** or optimism. It is common in brief interventions to encourage self-efficacy for change, rather than emphasizing helplessness or powerlessness. Optimism regarding the possibility of change is often embedded in effective motivational counseling.
- Ongoing followup. In addition to these six elements, effective use of brief intervention often includes repeated followup visits. At least two studies have found that a reduction in drinking occurs after the first followup visit (Elvy et al. 1988; Heather et al. 1987). However, even without the benefit of repeated followup, studies consistently document the occurrence of marked behavior change immediately following the brief intervention.

Source: Adapted from Miller and Sanchez 1994.

Tolerance, Intoxication, and Withdrawal

For each drug ever used, explore tolerance, intoxication, and withdrawal syndromes. Especially focus on opioid-related syndromes.

Tolerance is the need for markedly increased amounts of the substance to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of the substance.

- Has tolerance developed to any drugs of abuse? How has tolerance manifested in this patient? Has any decrease in tolerance occurred? Quantify tolerance by the amount used and/or the cost of drugs needed to achieve effects.
- What is the most of each substance the patient can consume in a 24-hour period now? What is the most ever consumed in a 24-hour period?

Intoxication and Overdose

- Explore symptoms of intoxication for each drug used.
- **Intoxication.** What was the patient's age at first intoxication? What drug(s) were involved in that intoxication? How have intoxication episodes progressed over time? Describe recent intoxication episodes.
- For opioids, has the patient experienced drowsiness ("nodding out"), slurred speech, impaired memory or attention, respiratory depression, and/or coma?
- **Overdose.** Have there been any episodes of intentional or nonintentional overdose with any drug or drug combinations? What symptoms did the individual have? What treatments were received? How did the episodes resolve?

Withdrawal

- **Withdrawal** is the characteristic withdrawal syndrome for the substance. The same (or a closely related) substance may be taken to relieve or avoid withdrawal symptoms. (The signs and symptoms of opioid withdrawal are shown in figure 3–7.)
- Describe withdrawal symptoms or syndromes the patient has ever experienced. What is the pattern of withdrawal symptoms? What relieves the symptoms (e.g., more of the drug and/or a cross-tolerant drug)? Describe the characteristics of withdrawal episodes over time.
- What signs of opioid withdrawal occurred after discontinuation of use (e.g., dysphoria, nausea or vomiting, aching muscles, tearing, rhinorrhea, dilated pupils, piloerection, sweating, diarrhea, yawning, fever, and insomnia)?
- What treatments for withdrawal or its complications have been received in the past?
- **Withdrawal complications.** Is there any history of withdrawal complications (e.g., seizures—from withdrawal with sedative-hypnotics or intoxication with stimulants or opioids**,** delirium tremens, hallucinations)? What treatment was received for these past complications, and what was the treatment response?

Relapse or Attempts at Abstinence

- Has the patient had a persistent desire or made unsuccessful efforts to cut down or control substance use? How many times has the patient attempted to become abstinent? How was the patient able to achieve abstinence? Quantify the longest time completely abstinent from all psychoactive drugs. What was going on during the time of abstinence? To what does the patient attribute his or her abstinence?
- What is the patient's relapse history? What happened to end any abstinent periods? What triggered or preceded relapses? What drug(s) did the patient use when relapsing? What pattern of use developed after the relapses? How did the patient's use patterns change over time with each relapse? Are there any life circumstances that would give clues to events precipitating either relapse or abstinence?
- Has the patient ever been abstinent from all psychoactive drugs for an extended period of time? When and for how long? What has been the longest time free of opioids in the past year, the past 5 years, and lifetime? What has been the longest time free of all psychoactive substances in the past year, the past 5 years, and lifetime? Has the patient switched from one addicting substance to another over time?

Treatment History—Addiction Treatment History

- What previous diagnoses—addiction, psychiatric, and medical—have been given to this patient?
- Describe all past attempts at detoxification. How many times has detoxification been tried? Was detoxification medically supervised? If so, how long were the detoxification treatments? What were the complications of

detoxification? What were the outcomes? How long after detoxification did the patient start using opioids again? Why?

- If the patient has ever been treated for addiction:
  - How many times has he or she received treatment? How long was each treatment?
  - What level(s) of care were received (detoxification, inpatient, residential, outpatient, sober-living environment, opioid maintenance therapy)? What treatments were received (group, individual, or family psychotherapy; relapse prevention; pharmacotherapy; education; cognitive-behavioral therapy; motivational enhancement therapy; others)? Was the focus of the treatment on psychiatric symptoms or addiction problems, or did the individual receive integrated addiction and psychiatric treatment services? How long was each treatment? Did the patient complete the recommended treatments? If not, why not?
  - Has the patient received pharmacotherapy for addiction? What previous treatment was received (e.g., brief medical detoxification, opioid maintenance therapy, disulfiram, naltrexone, or other medication therapy)? Has previous treatment been medical therapy alone or medical therapy in combination with comprehensive treatment interventions?
  - Was the patient compliant with previous drug and alcohol treatment, including prior opioid treatment programs? Did he or she use drugs and alcohol while in treatment? How long did she remain completely abstinent from all nonprescribed psychoactive drugs after each treatment? Which treatment was the most successful? Which one was least successful? What factors contributed to the success or failure of treatments?
- Has the patient had contact with Alcoholics Anonymous (AA), Narcotics Anonymous (NA), Cocaine Anonymous (CA), or other 12-Step recovery programs? Ask the patient to describe his or her involvement in those programs. How many meetings were attended? Did he or she ever get a sponsor and work the steps? Does he or she have a current sponsor? How frequent is meeting attendance now?
- Has the patient been involved in support groups other than 12-Step? If so, which ones? Ask the patient to describe the support groups and the level of his or her activities and involvement.

Psychiatric History

- Review of symptoms: What psychiatric symptoms has the patient ever experienced? Ask about depression, anxiety, irritability, agitation, delusions, hallucinations, mood swings, suicidal thoughts or attempts, homicidal thoughts or attempts, sleep disturbance, appetite or energy disturbance, memory loss, dissociation, etc. What current psychiatric complaints or symptoms does the patient have? Are they related to current drug use or inability to stop using?
- Were psychiatric symptoms present before, during, and/or after substance use? What effects did abstinence from other drugs and alcohol and/or compliance with maintenance treatment have on psychiatric symptoms? Has the patient ever had a substance-induced psychotic disorder, mood disorder, anxiety disorder, persisting perceptual disorder, persisting amnestic disorder, persisting dementia, or sexual dysfunction?
- Has the patient ever had contact with psychiatrists or psychologists? What were previous psychiatric diagnoses? What medications were provided?
- Has the patient ever been in psychotherapy? If so, what kind and for how long? Has he or she ever been hospitalized for psychiatric treatment? If so, what precipitated hospitalization?
- What psychotropic medications have been prescribed and what was the response to each? List current psychotropic medications, prescribers of each medication, and the patient's clinical response.

- Were other treatments recommended? Was the patient compliant? What has helped the most?
- What stressors and traumas have occurred throughout life? Was the patient ever physically, emotionally, and/or sexually abused, or traumatized in other ways? If so, at what age and under what circumstances? Has the patient ever discussed such trauma with a treatment provider or received treatment for these problems?

Family History

- Which biological relatives have a history of addiction, alcoholism, "drinking problems," "drug problems" (including prescription drug addiction), cirrhosis or other associated medical problems, depression, anxiety, sleep problems, attempted or completed suicide or homicide, psychiatric disorders or problems, overdoses, incarceration, criminal involvement, etc.? Have any family members been in recovery from addiction?
- What other illnesses have affected the patient's biological relatives?

Medical History

- Perform a detailed review of systems. What medical problems or complaints does the patient have now? Which ones are or could be related to drug or alcohol use?
- Past medical history: Ask about delirium tremens (DTs), withdrawal complications, or overdoses; tuberculosis or positive purified protein derivative (PPD) skin test, HIV infection, viral hepatitis (hepatitis A, B, C, D), syphilis, gonorrhea, pelvic inflammatory disease, or other sexually transmitted diseases (STDs); menstrual abnormalities, pregnancy or obstetric complications, spontaneous abortion; diabetes, thyroid disease, or other endocrine problem; cancer; hypertension, endocarditis, pericarditis, cardiomyopathy, congestive heart failure, ischemic heart disease, arrhythmia, heart murmur, mycotic aneurysm, thrombophlebitis; gastritis, ulcers, pancreatitis, hepatomegaly, hepatitis, or cirrhosis; pulmonary edema, chronic cough, pneumonia, lung abscess, chronic obstructive pulmonary disease; renal failure, renal calculi; sexual dysfunction; anemia, thrombocytopenia, neutropenia, lymphocytosis, or other blood disorders; lymphadenopathy; aseptic necrosis; osteoporosis; cellulitis, septic arthritis, osteomyelitis; brain, epidural, or subdural abscess; fungal meningitis; other infections; headaches, seizures, stroke, neuropathy, or other neurologic problems; physical trauma, accidents, and hospitalizations; any other medical complications of addiction. See figure 3–11 for a listing of selected medical disorders related to drug and alcohol use.
- For any female patient, is it possible that she is pregnant? When was her last menstrual period? Is she sexually active with men? What method of birth control does she use? Does she desire to become pregnant in the near future?
- Obtain the names and addresses of all other physicians currently providing care to the patient and obtain written consent to contact all treatment providers. Does the patient have a designated primary care physician? Is he or she being treated by a number of physicians? (See chapter 6 for a discussion of privacy and confidentiality laws and regulations pertaining to substance abuse treatment information.)
- What medications is the patient taking now, and for what reason? Who prescribed the current medications? What has been the response to medication? Ask the patient to list all current medications and complementary or alternative therapies, such as vitamins, minerals, herbs, and supplements.
- Explore the use, past and present, of addicting prescription drugs. What was the pattern of use of prescription drugs? Did the patient take the medications as prescribed, or more than prescribed, or in combination with alcohol or other drugs? Has the patient received prescriptions from several physicians? Has the patient ever "lost" prescriptions in order to obtain new ones, forged or

phoned in prescriptions, stolen prescription pads, split prescriptions with others, or otherwise misused prescription medications?

- Does the patient have pain problems? What pain treatments have been tried or recommended? Have opioid medications been prescribed? What was the response to various pain treatments? What is the level of pain now?

Sexual History

- Is the patient sexually active? How many sexual partners does the patient have? How long has he or she been involved with his or her current partner(s)? Quantify the number and gender of sexual partners over the patient's lifetime. Has the patient had sex with multiple partners or strangers? Has the patient had sex with males, females, or both?
- What specific sexual activities has the patient engaged in? Does he or she ever have sex without a condom or other barrier protection? Has he or she traded sex for money or drugs?
- Has the patient or any of his or her partners ever had or been treated for an STD? If so, which ones (syphilis, gonorrhea, HIV, chlamydia, or others)? How long ago were these treatments? How many times has the patient been treated for an STD?
- Does the patient have any current symptoms of an STD, such as genital discharge, pain, itching, sores, or lumps?
- Has the patient ever been hurt or abused by a sexual partner? Has he or she ever been sexually abused, molested, raped, or assaulted?
- Is sex satisfying for the patient? Does he or she have any problems with or concerns about his or her sexual activities or function?

Cost/Consequences of Drug Use

- What is the patient's current level of functioning in social, family or relationship, educational, occupational, legal, physical health, and mental health arenas?
- Has functioning been affected by drug use? If so, how? What financial, familial, social, emotional, occupational, legal, medical, or spiritual problems have occurred while the patient has been using drugs or as a result of having used drugs? Has the patient experienced legal problems, arrests, been charged with driving while intoxicated, had multiple divorces, marital discord, bankruptcy, fights, injuries, family violence, or suicidal thoughts? Describe specific problems and consequences.
- Has there been hazardous or impairing substance use? If so, describe specifics.
- Has a great deal of time been spent in activities necessary to obtain the substance, use the substance, or recover from its effects? Have important social, occupational, or recreational activities been given up or reduced because of substance use?
- Has there been continued use despite adverse physical and social consequences? Has the substance use continued despite knowledge of having persistent problems that are likely to have been caused or worsened by the substance? If so, give examples.

Compulsivity or Craving

- Does the patient report drug craving and/or urges to use? How does the patient deal with them?
- Does the patient obsess about using drugs? Is there a compulsive pattern to the drug use?

Control

- Has loss of consistent control over drug use occurred? Does the patient feel he or she has ever lost control over use, even one time? When did this first occur? What was the situation? What happened? Has the patient often taken a substance in larger amounts or over a longer period than was intended? Describe the evidence for loss of consistent control over use.

- If the patient does not think control has ever been lost, do others (family, friends, employers, physicians, or others) think differently?

Social and Recovery Environment

- What is the quality of recovery environment for this patient (supportive, nonsupportive, or toxic)? What has been the response of family, significant others, friends, employer, and others to the patient's problems? What is the existing problem as the spouse, partner, or significant other sees it? Have any of these individuals suggested that the patient may have an alcohol or drug problem? When did they first suggest this? What do others object to about the patient's drinking or drug use? What are their concerns or complaints?
- Is the patient's neighborhood, job, or profession a factor that does not support recovery?
- What is or has been the patient's support system? Have supportive individuals been involved in Al-Anon, Nar-Anon, or similar programs? Are they supportive of the patient's getting help? Who has been alienated?
- How many friends, family, or associates are partners in drinking or using? Are alcohol or other drugs present or used in the house where the patient lives? Who is drinking or using drugs in the patient's home? What addicting drugs, either prescribed or nonprescribed, are still at home now?

Insight, Motivation, Readiness to Change

- What is the patient's understanding of his or her problem? What does the patient understand about the disease of addiction?
- What Stage of Change is the patient in now: Precontemplation, Contemplation, Preparation, Action, Maintenance, Relapse? (See appendix G.) What stages has he or she passed through in the past? How responsive is he or she to motivational enhancement therapy?

Why Now?

- Why did the patient seek treatment or help at this time?
- Is treatment coerced or voluntary? What are the consequences if the patient does not seek help or complete treatment? How does the patient feel about these consequences?

Detection of Drugs in Urine and Other Samples

Physicians should become familiar with their laboratory's collection procedures, sample testing methodology, quality control and assurance procedures, and adulterant testing methodology. They must understand laboratory report forms and procedures, the drugs screened in a routine panel, other drug tests performed at the laboratory, sensitivity of tests, and cutoff levels for reporting positive or negative test results. A comprehensive discussion of urine drug testing in the primary care setting can be found in *Urine Testing in Primary Care: Dispelling the Myths & Designing Strategies* (Gourlay et al. 2002). It is advisable that physicians become acquainted with the laboratory director and other personnel who can answer questions and provide other useful information.

Initial screening typically utilizes an enzyme multiplied immunoassay test (EMIT), a radioimmunoassay (RIA), or a florescent polarization immunoassay (FPIA) test; each is based on antigen-antibody interactions and is highly sensitive for specific drugs. Gas chromatography with mass spectrometry (GC/MS) is a highly sensitive and specific test that is labor intensive and costly, and is generally used to confirm the results of screening tests.

Detection of a drug depends on usage factors (e.g., dose used, frequency of use, proximity of last use) and characteristics of the specific drug. Most common drugs of abuse (e.g.,

cocaine, methamphetamine, heroin, marijuana) or their metabolites are readily detectable in the urine. Recent alcohol use is detectable in saliva, breath, blood, and urine samples.

Morphine (the metabolite of heroin) is detected by commercially available urine testing; however, methadone will not be detected as an opiate on some drug tests, unless a methadone assay is specifically requested. Oxycodone will cross-react only at high concentrations. Buprenorphine does not cross-react with the detection procedures for methadone or heroin. Although buprenorphine and its metabolite are excreted in urine, routine screening for the presence of buprenorphine is not feasible until testing kits become commercially available; none were available at the time this document was prepared.

Low-potency benzodiazepines (e.g., diazepam and chlordiazepoxide) are readily detected in routine urine drug screens. However, clonazepam, flunitrazepam, alprazolam, and several other benzodiazepines may be undetected in urine samples. Since the combination of buprenorphine and benzodiazepines can be lethal (Reynaud et al. 1998*a*,*b*; Tracqui et al. 1998), it is essential to screen effectively for the recent use of benzodiazepines. It may be necessary to specifically request that a sample be evaluated for benzodiazepines that are not detected on routine drug screens.

Appendix F
Federation of State Medical Boards—
Model Policy Guidelines for Opioid Addiction Treatment in the Medical Office

SECTION I: PREAMBLE

The (name of board) recognizes that the prevalence of addiction to heroin and other opioids has risen sharply in the United States and that the residents of the State of (name of state) should have access to modern, appropriate and effective addiction treatment. The appropriate application of up-to-date knowledge and treatment modalities can successfully treat patients who suffer from opioid addiction and reduce the morbidity, mortality and costs associated with opioid addiction, as well as public health problems such as HIV, HBV, HCV and other infectious diseases. The Board encourages all physicians to assess their patients for a history of substance abuse and potential opioid addiction. The Board has developed these guidelines in an effort to balance the need to expand treatment capacity for opioid addicted patients with the need to prevent the inappropriate, unwise or illegal prescribing of opioids.

Until recently, physicians have been prohibited from prescribing and dispensing opioid medications in the treatment of opioid addiction, except within the confines of federally regulated opioid treatment programs. Because of the increasing number of opioid-addicted individuals and the associated public health problems, as well as the limited availability of addiction treatment programs, federal laws now enable qualified physicians to prescribe Schedule III-V medications approved by the Food and Drug Administration for office-based treatment of opioid addiction[1].

Physicians who consider office-based treatment of opioid addiction must be able to recognize the condition of drug or opioid addiction and

be knowledgeable about the appropriate use of opioid agonist, antagonist, and partial agonist medications. Physicians must also demonstrate required qualifications as defined under and in accordance with the "Drug Addiction Treatment Act of 2000" (DATA) (Public Law 106-310, Title XXXV, Sections 3501 and 3502) and obtain a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA), as authorized by the Secretary of HHS. In order to qualify for a waiver, physicians must hold a current license in the State of (name of state) and, at a minimum, meet one or more of the following conditions to be considered as qualified to treat opioid addicted patients in an office-based setting in this state:

- Subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
- Subspecialty board certification in addiction medicine from the American Osteopathic Association
- Addiction certification from the American Society of Addiction Medicine
- Completion of not less than 8 hours of training related to the treatment and management of opioid-dependent patients provided by the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, the American Psychiatric Association, or other organization approved by the board.
- Participation as an investigator in one or more clinical trials leading to the approval of a narcotic drug in Schedule III, IV, or V or a combination of such drugs for treatment of opioid addicted patients (must be evidenced by a statement submitted to the Secretary of Health and Human Services by the sponsor of such approved drug).
- Additional qualification criteria may be added through legislative enactment.

In addition to the waiver, physicians must have a valid DEA registration number and a DEA identification number that specifically authorizes such office-based treatment.

The waiver to provide addiction treatment under DATA is granted by the Secretary of HHS, presumably through SAMHSA, no later than 45 days after receipt of the physician's written notification. Upon request from SAMHSA, the Attorney General, presumably through DEA, will automatically assign the physician an identification number that will be used with the physician's DEA registration number. However, if SAMHSA has not acted on the physician's request for a waiver by the end of this 45-day period, DEA will automatically assign the physician an identification number.

Furthermore, if a physician wishes to prescribe or dispense narcotic drugs for maintenance or detoxification treatment on an emergency basis in order to facilitate the treatment of an individual patient before the 45-day waiting period has elapsed, the physician musty notify SAMHSA and the DEA of the physician's intent to provide such treatment.

The Board recognizes that new treatment modalities offer an alternative in the treatment of opioid addiction. Based on appropriate patient assessment and evaluation, it may be both feasible and desirable to provide office-based treatment of opioid addicted patients with Schedules III-V opioid medications approved for such use by the FDA and regulated in such use by Center for Substance Abuse Treatment (CSAT)/SAMHSA. Physicians are referred to the Buprenorphine Clinical Practice Guidelines, available at the CSAT/SAMHSA, Division of Pharmacologic Therapies, Second Floor, 1 Choke Cherry Road, Rockville, MD 20857; (301) 443-7614 or http://www.dpt.samhsa.gov/.

The medical recognition and management of opioid addiction should be based upon current knowledge and research and includes the use of both pharmaceutical and non-pharmaceutical modalities. Prior to initiating

treatment, physicians should be knowledgeable about addiction treatment and all available pharmacologic treatment agents as well as available ancillary services to support both the physician and patient. In order to undertake treatment of opioid addicted patients, in accordance with these guidelines, physicians must demonstrate a capacity to refer patients for appropriate counseling and other ancillary services.

The (state medical board) is obligated under the laws of the State of (name of state) to protect the public health and safety. The Board recognizes that inappropriate prescribing of controlled substances, including opioids, may lead to drug diversion and abuse by individuals who seek them for other than legitimate medical use. Physicians must be diligent in preventing the diversion of drugs for illegitimate and nonmedical uses.

Qualified physicians need not fear disciplinary action from the Board or other state regulatory or enforcement agency for appropriate prescribing, dispensing or administering approved opioid drugs in Schedules III, IV, or V, or combinations thereof, for a legitimate medical purpose in the usual course of opioid addiction treatment. The Board will consider appropriate prescribing, ordering, administering, or dispensing of these medications for opioid addiction to be for a legitimate medical purpose if based on accepted scientific knowledge of the treatment of opioid addiction and in compliance with applicable state and federal law.

The Board will determine the appropriateness of prescribing based on the physician's overall treatment of the patient and on available documentation of treatment plans and outcomes. The goal is to document and treat the patient's addiction while effectively addressing other aspects of the patient's functioning, including physical, psychological, medical, social and work-related factors. The following guidelines are not intended to define complete or best practice, but rather to communicate what the Board considers to be within the boundaries of accepted professional practice.

SECTION II: GUIDELINES

The Board has adopted the following guidelines when evaluating the documentation and treatment of opioid addiction under DATA:

Compliance With Controlled Substances Laws and Regulations

Generally, to prescribe and dispense Schedules III-V opioid medications for the treatment of opioid addiction under DATA, the physician must be licensed in the state, have a valid DEA controlled substances registration and identification number, comply with federal and state regulations applicable to controlled substances, and have a current waiver issued by SAMHSA. To obtain this waiver, the physician must submit written notification to the Secretary of HHS of their intent to provide this treatment modality, certifying the physician's qualifications and listing his/her DEA registration number. SAMHSA will then notify DEA whether a waiver has been granted. If SAMHSA grants the physician a waiver, DEA will issue the qualifying physician an identification number. In addition to these requirements, the DATA limits the number of patients that a physician or a group practice is permitted to treat to 30. This numerical limitation may be changed by regulation in the future.

Physicians are specifically prohibited from delegating prescribing opioids for detoxification and/or maintenance treatment purposes to non-physicians. Physicians are referred to DEA regulations (21CFR, Part 1300 to end) and the DEA Physician's Manual www.deadiversion.usdoj.gov and (any relevant documents issued by the state medical board) for specific rules governing issuance of controlled substances prescriptions as well as applicable state regulations.

Evaluation of the Patient

A recent, complete medical history and physical examination must be documented in

the medical record. The medical record should document the nature of the patient's addiction(s), evaluate underlying or coexisting diseases or conditions, the effect on physical and psychological function, and history of substance abuse and any treatments therefor. The medical record should also document the suitability of the patient for office-based treatment based upon recognized diagnostic criteria.[2]

DSM-IV-TR Substance Dependence Criteria [3]

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- tolerance, as defined by either of the following:
  - a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or
  - markedly diminished effect with continued use of the same amount of the substance
- withdrawal, as manifested by either of the following:
  - the characteristic withdrawal syndrome for the substance, or
  - the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
- the substance is often taken in larger amounts or over longer period than was intended
- there is a persistent desire or unsuccessful efforts to cut down or control substance use
- a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects
- important social, occupational or recreational activities are given up or reduced because of substance use
- the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Treatment Plan

The written treatment plan should state objectives that will be used to determine treatment success, such as freedom from intoxication, improved physical function, psychosocial function and compliance and should indicate if any further diagnostic evaluations are planned, as well as counseling, psychiatric management or other ancillary services. This plan should be reviewed periodically. After treatment begins, the physician should adjust drug therapy to the individual medical needs of each patient. Treatment goals, other treatment modalities or a rehabilitation program should be evaluated and discussed with the patient. If possible, every attempt should be made to involve significant others or immediate family members in the treatment process, with the patient's consent. The treatment plan should also contain contingencies for treatment failure (i.e., due to failure to comply with the treatment plan, abuse of other opioids, or evidence that the Schedules III-V medications are not being taken).

Informed Consent and Agreement for Treatment

The physician should discuss the risks and benefits of the use of these approved opioid medications with the patient and, with appropriate consent of the patient, significant

other(s), family members, or guardian. The patient should receive opioids from only one physician and/or one pharmacy when possible. The physician should employ the use of a written agreement between physician and patient addressing such issues as (1) alternative treatment options; (2) regular toxicologic testing for drugs of abuse and therapeutic drug levels (if available and indicated); (3) number and frequency of all prescription refills and (4) reasons for which drug therapy may be discontinued (i.e.; violation of agreement).

Periodic Patient Evaluation

Patients should be seen at reasonable intervals (at least weekly during initial treatment) based upon the individual circumstance of the patient. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of treatment plan, and to assess how the patient is handling the prescribed medication. Once a stable dosage is achieved and urine (or other toxicologic) tests are free of illicit drugs, less frequent office visits may be initiated (monthly may be reasonable for patients on a stable dose of the prescribed medication(s) who are making progress toward treatment objectives). Continuation or modification of opioid therapy should depend on the physician's evaluation of progress toward stated treatment objectives such as (1) absence of toxicity (2) absence of medical or behavioral adverse effects (3) responsible handling of medications (4) compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy and/or other psychosocial modalities) and (5) abstinence from illicit drug use. If reasonable treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continued treatment.

Consultation

The physician should refer the patient as necessary for additional evaluation and treatment in order to achieve treatment objectives. The physician should pursue a team approach to the treatment of opioid addiction, including referral for counseling and other ancillary services. Ongoing communication between the physician and consultants is necessary to ensure appropriate compliance with the treatment plan. This may be included in the formal treatment agreement between the physician and patient. Special attention should be given to those patients who are at risk for misusing their medications and those whose living or work arrangements pose a risk for medication misuse or diversion. The management of addiction in patients with comorbid psychiatric disorders requires extra care, monitoring, documentation and consultation with or referral to a mental health professional.

Medical Records

The prescribing physician should keep accurate and complete records to include (1) the medical history and physical examination; (2) diagnostic, therapeutic and laboratory results; (3) evaluations and consultations; (4) treatment objectives; (5) discussion of risks and benefits; (6) treatments; (7) medications (including date, type, dosage, and quantity prescribed and/or dispensed to each patient); (8) a physical inventory of all Schedules III, IV, and V controlled substances on hand that are dispensed by the physician in the course of maintenance or detoxification treatment of an individual; (9) instructions and agreements; and (10) periodic reviews. Records should remain current and be maintained in an accessible manner and readily available for review. The physician must adhere to the special confidentiality requirements of 42CFR, Part 2, which apply to the treatment of drug and alcohol addiction, including the prohibition against release of records or other information, except pursuant to a proper patient consent or court order in full compliance with 42CFR2, or the Federal or State officials listed in 42CFR2, or in cases of true medical emergency or for the mandatory reporting of child abuse.

SECTION III: DEFINITIONS

For the purposes of these guidelines, the following terms are defined as follows:

Addiction: A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving.

Agonists: Agonist drugs are substances that bind to the receptor and produce a response that is similar in effect to the natural ligand that would activate it. Full mu opioid agonists activate mu receptors, and increasing doses of full agonists produce increasing effects. Most opioids that are abused, such as morphine and heroin are full mu opioid agonists.

"Approved Schedule III-V Opioids": Opioids referred to by the DATA, specifically approved by the FDA for treatment of opioid dependence or addiction.

Antagonists: Antagonists bind to but do not activate receptors. They prevent the receptor from being activated by an agonist compound. Examples of opioid antagonists are naltrexone and naloxone.

Maintenance Treatment: Maintenance treatment means the dispensing for a period in excess of 21 days of an opioid medication(s) at stable dosage levels in the treatment of an individual for dependence upon heroin or other morphine-like drugs.

Opioid Dependence: A maladaptive pattern of substance use, leading to clinically significant impairment or distress, manifested by 3 or more of the following, occurring at any time in the same 12-month period:

- A need for markedly increased amounts of the substance to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of substance;
- The characteristic withdrawal syndrome for the substance or the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;
- The substance was taken in larger amounts or over a longer period of time than was intended;
- There is a persistent desire or unsuccessful efforts to cut down or control substance use;
- Significant time is spent on activities to obtain the substance, use the substance, or recover from its effects;
- Important social, occupational, or recreational activities are discontinued or reduced because of substance use;
- Substance use is continued despite knowledge of having a persistent physical or psychological problem that is caused or exacerbated by the substance.

Opioid Drug: Opioid drug means any drug having an addiction-forming or addiction-sustaining liability similar to morphine or being capable of conversion into a drug having such addiction-forming or addiction sustaining liability. (this is referred to as an opiate in the Controlled Substances Act)

Opioid Treatment Program (OTP) (sometimes referred to as a methadone clinic or narcotic treatment program): Opioid treatment program means a licensed program or practitioner engaged in the treatment of opioid addicted patients with approved Scheduled II opioids (methadone and/or LAAM).

Partial Agonists: Partial agonists occupy and activate receptors. At low doses, like full agonists, increasing doses of the partial agonist produce increasing effects. However, unlike full agonists, the receptor-activation produced by a partial agonist reaches a plateau over which increasing doses do not produce an increasing effect. The plateau may have the effect of limiting the partial agonist's therapeutic activity as well as its toxicity.

Buprenorphine is an example of a partial agonist.

Physical Dependence: A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Qualified Physician: A physician, licensed in the State of (name of state) who holds a current waiver issued by SAMHSA (as authorized by the Secretary of HHS) and meets one or more of the conditions set forth in Section 1. In addition, a physician must have a valid DEA registration and identification number authorizing the physician to conduct office-based treatment.

Substance Abuse: A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:

- Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home;
- Recurrent substance use in situations in which it is physically hazardous;
- Recurrent substance-related legal problems;
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

Tolerance: A state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time.

Waiver: A documented authorization from the Secretary of HHS issued by SAMHSA under the DATA that exempts qualified physicians from the rules applied to OTPs. Implementation of the waiver includes possession of a valid DEA certificate with applicable suffix.

Footnotes:

[1] Drug Addiction Treatment Act of 2000, Public Law 106-310, Title XXXV, Section 3501 and 3502.

[2] Buprenorphine Clinical Practice Guidelines, Table 3-1.

[3] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision, Washington, D.C.

This document can be found on model policy guidelines at http://www.fsmb.org, then click on policy documents. The recommendations contained herein were adopted as policy by the House of Delegates of the Federation of State Medical Boards of the United States, Inc., April 2002.

Appendix G
Stages of Change

As an important component of effective treatment planning, physicians may find it helpful to determine which stage of change characterizes the patient. There are six stages of change: precontemplation, contemplation, preparation, action, maintenance, and relapse. Patients can be conceptualized as moving along a continuum marked by these stages, each of which is described below. Readiness to change and stage of change can be evaluated by interview and instruments such as the Stages of Change Readiness and Treatment Eagerness Scale (Miller and Tonigan 1996). Stages of change are clearly linked to a patient's motivation. It may be possible for a physician to increase motivation (e.g., through motivational enhancement therapy) and thus help a patient move from an early stage of change (e.g., contemplation) to a more active and healthy stage (e.g., action). The discussion of Stages of Changes below is excerpted from Center for Substance Abuse Treatment (CSAT) TIP 35, *Enhancing Motivation for Change in Substance Abuse Treatment* (CSAT 1999*b*). (See http://www.kap.samhsa.gov/products/manuals/index.htm.)

Transtheoretical Model of Stages of Change

It is important to note that the change process is cyclical, and individuals typically move back and forth between the stages and cycle through the stages at different rates. In one individual, this movement through the stages can vary in relation to different behaviors or objectives. Individuals can move through stages quickly. Sometimes, they move so rapidly that it is difficult to pinpoint where they are because change is a dynamic process. It is not uncommon, however, for individuals to linger in the early stages.

For most substance-using individuals, progress through the stages of change is circular or spiral in nature, not linear. In this model, recurrence is a normal event because many clients cycle through the

different stages several times before achieving stable change. The six stages and the issue of relapse are described below.

Precontemplation

During the precontemplation stage, substance-using individuals are not considering change and do not intend to change behaviors in the foreseeable future. They may be partly or completely unaware that a problem exists, that they have to make changes, and that they may need help in this endeavor. Alternatively, they may be unwilling or too discouraged to change their behavior. Individuals in this stage usually have not experienced adverse consequences or crises because of their substance use and often are not convinced that their pattern of use is problematic or even risky.

Contemplation

As these individuals become aware that a problem exists, they begin to perceive that there may be cause for concern and reasons to change. Typically, they are ambivalent, simultaneously seeing reasons to change and reasons not to change. Individuals in this stage are still using substances, but they are considering the possibility of stopping or cutting back in the near future. At this point, they may seek relevant information, reevaluate their substance use behavior, or seek help to support the possibility of changing behavior. They typically weigh the positive and negative aspects of making a change. It is not uncommon for individuals to remain in this stage for extended periods, often for years, vacillating between wanting and not wanting to change.

Preparation

When an individual perceives that the envisioned advantages of change and adverse consequences of substance use outweigh any positive features of continuing use at the same level and maintaining the status quo, the decisional balance tips in favor of change. Once instigation to change occurs, an individual enters the preparation stage, during which commitment is strengthened. Preparation entails more specific planning for change, such as making choices about whether treatment is needed and, if so, what kind. Preparation also entails an examination of one's perceived capabilities—or self-efficacy—for change. Individuals in the preparation stage are still using substances, but typically they intend to stop using very soon. They may have already attempted to reduce or stop use on their own or may be experimenting now with ways to quit or cut back (DiClemente and Prochaska 1998). They begin to set goals for themselves and make commitments to stop using, even telling close associates or significant others about their plans.

Action

Individuals in the action stage choose a strategy for change and begin to pursue it. At this stage, clients are actively modifying their habits and environment. They are making drastic lifestyle changes and may be faced with particularly challenging situations and the physiological effects of withdrawal. Clients may begin to reevaluate their own self-image as they move from excessive or hazardous use to nonuse or safe use. For many, the action stage can last from 3 to 6 months following termination or reduction of substance use. For some, it is a honeymoon period before they face more daunting and longstanding challenges.

Maintenance

During the maintenance stage, efforts are made to sustain the gains achieved during the action stage. Maintenance is the stage at which individuals work to sustain sobriety and prevent recurrence (Marlatt and Gordon 1985). Extra precautions may be necessary to keep from reverting to problematic behaviors. Individuals learn how to detect and guard

against dangerous situations and other triggers that may cause them to use substances again. In most cases, individuals attempting long-term behavior change do return to use at least once and revert to an earlier stage (Prochaska and DiClemente 1992). Recurrence of symptoms can be viewed as part of the learning process. Knowledge about the personal cues or dangerous situations that contribute to recurrence is useful information for future change attempts. Maintenance requires prolonged behavioral change—by remaining abstinent or moderating consumption to acceptable, targeted levels—and continued vigilance for a minimum of 6 months to several years, depending on the target behavior (Prochaska and DiClemente 1992).

Relapse

Most individuals do not immediately sustain the new changes they are attempting to make, and a return to substance use after a period of abstinence is the rule rather than the exception (Brownell et al. 1986; Prochaska and DiClemente 1992). These experiences contribute information that can facilitate or hinder subsequent progression through the stages of change. *Recurrence*, often referred to as relapse, is the event that triggers the individual's return to earlier stages of change and recycling through the process. Individuals may learn that certain goals are unrealistic, certain strategies are ineffective, or certain environments are not conducive to successful change. Most substance users will require several revolutions through the stages of change to achieve successful recovery (DiClemente and Scott 1997). After a return to substance use, clients usually revert to an earlier change stage—not always to maintenance or action, but more often to some level of contemplation. They may even become precontemplators again, temporarily unwilling or unable to try to change soon. Resuming substance use and returning to a previous stage of change should not be considered a failure and need not become a disastrous or prolonged recurrence. A recurrence of symptoms does not necessarily mean that a client has abandoned a commitment to change.

Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 8D)

INSTRUCTIONS: Please read the following statements carefully. Each one describes a way that you might (or might not) feel *about your drug use*. For each statement, circle one number from 1 to 5 to indicate how much you agree or disagree with it *right now*. Please circle one and only one number for every statement.

	NO! Strongly Disagree	No Disagree	? Undecided or Unsure	Yes Agree	YES! Strongly Agree
1. I really want to make changes in my use of drugs.	1	2	3	4	5
2. Sometimes I wonder if I am an addict.	1	2	3	4	5
3. If I don't change my drug use soon, my problems are going to get worse.	1	2	3	4	5
4. I have already started making some changes in my use of drugs.	1	2	3	4	5
5. I was using drugs too much at one time, but I've managed to change that.	1	2	3	4	5
6. Sometimes I wonder if my drug use is hurting other people.	1	2	3	4	5
7. I have a drug problem.	1	2	3	4	5
8. I'm not just thinking about changing my drug use, I'm already doing something about it.	1	2	3	4	5
9. I have already changed my drug use, and I am looking for ways to keep from slipping back to my old pattern.	1	2	3	4	5
10. I have serious problems with drugs.	1	2	3	4	5
11. Sometimes I wonder if I am in control of my drug use.	1	2	3	4	5
12. My drug use is causing a lot of harm.	1	2	3	4	5
13. I am actively doing things now to cut down or stop my use of drugs.	1	2	3	4	5
14. I want help to keep from going back to the drug problems that I had before.	1	2	3	4	5
15. I know that I have a drug problem.	1	2	3	4	5
16. There are times when I wonder if I use drugs too much.	1	2	3	4	5
17. I am a drug addict.	1	2	3	4	5
18. I am working hard to change my drug use.	1	2	3	4	5
19. I have made some changes in my drug use, and I want some help to keep from going back to the way I used before.	1	2	3	4	5

Source: Miller and Tonigan 1996. SOCRATES 8D and SOCRATES 8D Scoring Sheet. Center on Alcoholism, Substance Abuse, and Addictions (CASAA), Assessment Instruments. Available at http://casaa.unm.edu/inst/inst.html. Reprinted with permission.

SOCRATES Scoring Form (19-Item Version 8.0)

Transfer the client's answers from questionnaire (see note below):

	Recognition	Ambivalence	Taking Steps
	1 _____	2 _____	
	3 _____		4 _____
			5 _____
		6 _____	
	7 _____		8 _____
			9 _____
	10 _____	11 _____	
	12 _____		13 _____
			14 _____
	15 _____	16 _____	
	17 _____		18 _____
			19 _____
TOTALS	Re _____	Am _____	Ts _____
Possible Range:	7–35	4–20	8–40

SOCRATES Profile Sheet (19-Item Version 8A)

INSTRUCTIONS: From the SOCRATES Scoring Form (19-Item Version) transfer the total scale scores into the empty boxes at the bottom of the Profile Sheet. Then for each scale, CIRCLE the same value above it to determine the decile range.

DECILE SCORES	Recognition	Ambivalence	Taking Steps
90 Very High		19–20	39–40
80		18	37–38
70 High	35	17	36
60	34	16	34–35
50 Medium	32–33	15	33
40	31	14	31–32
30 Low	29–30	12–13	30
20	27–28	9–11	26–29
10 Very Low	7–26	4–8	8–25
RAW SCORES (from Scoring Sheet)	Re=	Am=	Ts=

These interpretive ranges are based on a sample of 1,726 adult men and women presenting for treatment of alcohol problems through Project MATCH. Note that individual scores are therefore being ranked as low, medium, or high *relative to people already presenting for alcohol treatment*.

Guidelines for Interpretation of SOCRATES-8 Scores

Using the SOCRATES Profile Sheet, circle the client's raw score within each of the three scale columns. This provides information as to whether the client's scores are low, average, or high *relative to individuals already seeking treatment for alcohol problems*. The following are provided as general guidelines for interpretation of scores, but it is wise in an individual case also to examine individual item responses for additional information.

RECOGNITION

HIGH scorers directly acknowledge that they are having problems related to their drinking, tending to express a desire for change and to perceive that harm will continue if they do not change.

LOW scorers deny that alcohol is causing them serious problems, reject diagnostic labels such as "problem drinker" and "alcoholic," and do not express a desire for change.

AMBIVALENCE

HIGH scorers say that they sometimes wonder if they are in control of their drinking, are drinking too much, are hurting other individuals, and/or are alcoholic. Thus a high score reflects ambivalence or uncertainty. A high score here reflects some openness to reflection, as might be particularly expected in the contemplation stage of change.

LOW scorers say that *they do not wonder* whether they drink too much, are in control, are hurting others, or are alcoholic. Note that an individual may score low on ambivalence *either* because they "know" their drinking is causing problems (high Recognition), *or* because they "know" that they do not have drinking problems (low Recognition). Thus a low Ambivalence score should be interpreted in relation to the Recognition score.

TAKING STEPS

HIGH scorers report that they are already doing things to make a positive change in their drinking, and may have experienced some success in this regard. Change is underway, and they may want help to persist or to prevent backsliding. A high score on this scale has been found to be predictive of successful change.

LOW scorers report that they are not currently doing things to change their drinking and have not made such changes recently.

Resources for More Information

- Recovery Attitude and Treatment Evaluator (RAATE) (Mee-Lee 1988). http://www.niaaa.nih.gov/publications/raate.htm
- University of Rhode Island Change Assessment (URICA) (McConnaughy et al. 1983). http://www.uri.edu/research/cprc/Measures/urica.htm
- SOCRATES (Miller and Tonigan 1996) http://casaa.unm.edu/inst/forms/socratesv8.pdf
- Readiness to Change Questionnaire (Rollnick et al. 1992). http://www.niaaa.nih.gov/publications/rtcq.htm http://www.dva.gov.au/health/provider/care_plans/change.htm

Appendix H
Sample Treatment Agreement/Contract

Treatment agreements/contracts are often employed in the treatment of addiction to make explicit the expectations regarding patient cooperation and involvement in the treatment process. On the following page is a sample addiction treatment agreement/contract that may be a useful tool in working with patients in an office-based setting.

As a participant in the buprenorphine protocol for treatment of opioid abuse and dependence, I freely and voluntarily agree to accept this treatment agreement/contract, as follows:

I agree to keep, and be on time to, all my scheduled appointments with the doctor and his/her assistant.

I agree to conduct myself in a courteous manner in the physician's office.

I agree not to arrive at the office intoxicated or under the influence of drugs. If I do, the doctor will not see me, and I will not be given any medication until my next scheduled appointment.

I agree not to sell, share, or give any of my medication to another individual. I understand that such mishandling of my medication is a serious violation of this agreement and would result in my treatment being terminated without recourse for appeal.

I agree not to deal, steal, or conduct any other illegal or disruptive activities in the doctor's office.

I agree that my medication (or prescriptions) can be given to me only at my regular office visits. Any missed office visits will result in my not being able to get medication until the next scheduled visit.

I agree that the medication I receive is my responsibility and that I will keep it in a safe, secure place. I agree that lost medication will not be replaced regardless of the reasons for such loss.

I agree not to obtain medications from any physicians, pharmacies, or other sources without informing my treating physician. I understand that mixing buprenorphine with other medications, especially benzodiazepines such as valium and other drugs of abuse, can be dangerous. I also understand that a number of deaths have been reported among individuals mixing buprenorphine with benzodiazepines.

I agree to take my medication as the doctor has instructed and not to alter the way I take my medication without first consulting the doctor.

I understand that medication alone is not sufficient treatment for my disease, and I agree to participate in the patient education and relapse prevention programs, as provided, to assist me in my treatment.

Printed Name	Signature	Date

Appendix I
Glossary

21 C.F.R. Part 291
Code of Federal Regulations (C.F.R.) that, among other things, sets standards for narcotic treatment and use of methadone.

42 C.F.R. Part 2
Federal Regulation concerning confidentiality of alcohol and drug abuse patient treatment records.

42 C.F.R. Part 8
Federal Regulation concerning dispensing of drugs through opioid treatment programs.

Addiction
A *behavioral* syndrome characterized by the repeated, compulsive seeking or use of a substance despite adverse social, psychological, and/or physical consequences. Addiction is often (but not always) accompanied by physical dependence, a withdrawal syndrome, and tolerance.

Alcoholism
A pattern of compulsive use of alcohol in which individuals devote substantial periods of time to obtaining and consuming alcoholic beverages despite adverse psychological or physical consequences, e.g., depression, blackouts, liver disease, or other consequences. *(*Adapted from *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., *Text Revision* [*DSM-IV-TR*].*)*

Antagonist
Substance that tends to nullify the effect of another (e.g., a drug that binds to a receptor without eliciting a response).

AUDIT
Alcohol **U**se **D**isorders **I**dentification **T**est. A screening tool for identification of alcohol use disorders.

Biopsychosocial
Combining biological, psychological, and social concerns or effects.

Buprenex® (Generic: buprenorphine)
Injectable formulation of the Schedule III narcotic (opioid) partial agonist buprenorphine. Approved for use as an analgesic. Not approved for use in the treatment of opioid addiction.

Buprenorphine
An opioid partial agonist that is a synthetic derivative of thebaine. Two sublingual formulations of buprenorphine, the Schedule III pharmaceuticals Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone), received Food and Drug Administration (FDA) approval in October 2000 for use in the treatment of opioid addiction. Buprenex®, an injectable formulation of buprenorphine, has previously been available in the United States and is approved for use as a parenteral analgesic.

Buprenorphine/naloxone
Drug combination; see separate definitions and brand name Suboxone®.

CAGE-AID
CAGE Questionnaire **A**dapted to **I**nclude **D**rugs.

CAGE Questionnaire
A screening tool for identification of alcohol use disorders (questions use words beginning with letters **C, A, G, a**nd **E** consecutively).

Children's Health Act of 2000 (P.L. 106-310)
Legislation (Public Law) that authorizes expanded research and services for a variety of childhood health problems, reauthorizes programs of the Substance Abuse and Mental Health Services Administration (SAMHSA), addresses the problem of youth substance abuse and the violence associated with it, and works to improve the health and safety of children in child care. Title XXXV of the Children's Health Act is the Drug Addiction Treatment Act of 2000 (DATA 2000), which authorizes qualifying physicians to treat opioid addiction in clinical settings other than the Opioid Treatment Program (OTP) setting.

CINA
Clinical **I**nstitute **N**arcotic **A**ssessment Scale for Withdrawal. An interview and observation tool for assessing opioid withdrawal signs and symptoms.

COWS
Clinical **O**piate **W**ithdrawal **S**cale. An interview and observation tool for assessing opioid withdrawal signs and symptoms.

DAST 10
Drug **A**buse **S**creening **T**est. A questionnaire tool for identification of drug and alcohol use disorders.

DATA 2000
See **D**rug **A**ddiction **T**reatment **A**ct of 2000.

Dependence
A condition manifested as a characteristic set of withdrawal signs and symptoms upon reduction, cessation, or loss of the active compound at cell receptors (a withdrawal syndrome).

Drug Addiction Treatment Act of 2000
Title XXXV of the Children's Health Act of 2000. The Drug Addiction Treatment Act of 2000 (DATA 2000) establishes a waiver authority for qualifying physicians to prescribe or dispense specially approved Schedule III, IV, and V narcotic medications for the treatment of opioid addiction in clinical settings other than the Opioid Treatment Program setting.

HIPAA
Health **I**nsurance **P**ortability and **A**ccountability **A**ct.

LAAM

Closely related to methadone, the synthetic compound levo-alpha-acetyl-methadol or LAAM (Brand name: ORLAMM®), has an even longer duration of action (from 48 to 72 hours) than methadone, permitting a reduction in frequency of use. In 1994, it was approved as a Schedule II treatment drug for narcotic addiction. Both methadone and LAAM have high abuse potential. Their acceptability as narcotic treatment drugs is predicated on their ability to substitute for heroin, the long duration of action, and their mode of oral administration.

MAST

Michigan **A**lcohol **S**creening **T**est. A questionnaire tool for identification of alcohol use disorders.

MCV

Mean corpuscular volume.

Methadone

A Schedule II synthetic opioid with pharmacologic actions similar to morphine and heroin; almost equally addictive. Approved for use in the treatment of opioid addiction in federally regulated Opioid Treatment Programs. May be administered orally, intramuscularly, and subcutaneously.

Monotherapy

Therapy using one drug or approach.

Morphine

Most active narcotic alkaloid of opium. Has powerful analgesic action; abuse leads to dependence.

Mu agonist

A drug that has affinity for and stimulates physiologic activity at mu opioid cell receptors. See also opioid full agonist.

Mu opioid receptor

A receptor on the surface of brain cells that mediates opioid analgesia, tolerance, and addiction through drug-induced activation. When an opioid agonist, or partial agonist (e.g., buprenorphine), binds to a mu opioid receptor, a series of other proteins associated with the mu receptor-signalling pathway becomes activated. Other opioid receptors are the delta and kappa receptors.

Naloxone

Brand name: Narcan®. An opioid antagonist, similar to naltrexone, that works by blocking opioid receptors in the brain, thereby blocking the effects of opioid full agonists (e.g., heroin, morphine) and partial agonists (e.g., buprenorphine).

Naltrexone

Naltrexone, a narcotic antagonist, works by blocking opioid receptors in the brain and therefore blocking the effects of opioid full agonists (e.g., heroin, morphine) and partial agonists (e.g., buprenorphine).

NATA

Narcotic **A**ddict **T**reatment **A**ct.

Needle embolization

Blood clot caused by use of a needle. If dislodged, the clot may cause death.

Nonopioid

Drug or compound not related to natural or synthetic opium and related alkaloids.

OAT

Opioid **A**gonist **T**reatment.

Opioids

Drugs that are derived naturally from the flower of the opium poppy plant (e.g., morphine and heroin) and those that are synthetically produced in the lab (e.g., methadone and oxycodone).

Used therapeutically to treat pain, but also produce a sensation of euphoria—the narcotic "high." Repeated misuse and abuse of opioids often leads to dependence and addiction.

Opioid full agonist
Drugs that have affinity for and stimulate physiologic activity at opioid cell receptors (mu, kappa, and delta) that are normally stimulated by naturally occurring opioids. Repeated administration often leads to dependence and addiction.

Opioid partial agonist
Drugs that can both activate and block opioid receptors, depending on the clinical situation. Partial agonists have properties of both agonists and antagonists. The mu agonist properties of partial agonists reach a maximum at a certain dose and do not continue to increase with increasing doses of the partial agonist. This is termed the ceiling effect. The ceiling effect limits the abuse potential and untoward side effects of opioid partial agonists. The Schedule III medication buprenorphine is an opioid partial agonist.

Parenteral
Not through the gastrointestinal route; for instance, given via intramuscular or intravenous injection.

Pharmacodynamics
Study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including correlation of these actions and effects with the drugs' chemical structure.

Pharmacokinetics
Study of the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Pharmacotherapy
Treatment of disease by using medicines.

Polysubstance abuse
Concurrent use or abuse of multiple substances (e.g., drinking alcohol as well as smoking tobacco, snorting cocaine, inhaling glue fumes).

Psychosocial
Combining psychological and social aspects.

SMAST
Short **M**ichigan **A**lcohol **S**creening **T**est. Shortened, self-administered version of the MAST alcohol use disorder screening tool.

SOWS
Subjective **O**pioid **W**ithdrawal **S**cale. Self-administered scale for grading opioid withdrawal symptoms.

Sublingual
Under the tongue.

Suboxone®
Brand name for the Schedule III sublingual formulation of buprenorphine combined with naloxone. Received FDA approval in October 2000 for use in the treatment of opioid addiction. Naloxone is added to the formulation to decrease the likelihood of abuse of the combination via the parenteral route.

Subutex®
Brand name for the Schedule III sublingual formulation of buprenorphine. Received FDA approval in October 2000 for use in the treatment of opioid addiction.

Talc granulomatosis
Formation of granulomas (small nodules) as a chronic inflammatory response, in the lungs or other organs, in this case to talc or other fine powder. Talc granulomatosis may occur in drug users because many injected drugs have been adulterated with an inert substance (such as talcum powder) to cut or dilute the amount of drug.

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Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction

This Treatment Improvement Protocol (TIP), *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*, provides consensus- and evidence-based treatment guidance for the use of buprenorphine, a new option for the treatment of opioid addiction. The goal of this TIP is to provide physicians with information they can use to make practical and informed decisions about the use of buprenorphine to treat opioid addiction. These guidelines address the pharmacology and physiology of opioids, opioid addiction, and treatment with buprenorphine; describe patient assessment and the choice of opioid addiction treatment options; provide detailed treatment protocols for opioid withdrawal and maintenance therapy with buprenorphine; and include information on the treatment of special populations, e.g., pregnant women, adolescents, and polysubstance users. This TIP represents another step by the Center for Substance Abuse Treatment (CSAT) toward its goal of bringing national leaders together to improve substance use disorder treatment in the United States.

Collateral Products
Based on TIP 40

Quick Guide for Physicians

DHHS Publication No. (SMA) 04-3939
Printed 2004

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment

Psychopharmacologic Drugs Advisory Committee
March 21, 2013

REFERENCE MATERIALS LIST

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